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Twenty-second day of October 2004

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**PROVISIONAL SPECIFICATION**

**for the invention entitled:**

**"Modulation of Hyaluronan Synthase"**

**The invention is described in the following statement:**

- 1 -

## MODULATION OF HYALURONAN SYNTHASE

### BACKGROUND OF THE INVENTION

#### 5 FIELD OF THE INVENTION

The present invention provides compositions and methods for modulating the expression of genetic material encoding hyaluronan synthase (HAS). In particular, the present invention relates to compounds which hybridize or otherwise interact with nucleic acid molecules encoding HAS and particularly HAS isoforms HAS1, HAS2 and HAS3 or with nucleic acid molecules required for or which facilitate expression of HAS-encoding material thereby reducing expression of the genetic material. These compounds include nucleic acid molecules, ranging in size from oligonucleotides to full length sequences and include complexes comprising RNAi or ribonuclease-type molecules. Such compounds are exemplified to modulate cellular proliferation, and are useful in the prophylaxis and/or treatment of inflammatory disorders, such as but not limited to cancer and arthritis. It will be understood, however, that the compounds can be used for any other condition in which hyaluronan (HA) is involved.

#### 20 DESCRIPTION OF THE PRIOR ART

Bibliographic details of the publications referred to in this specification are also collected at the end of the description.

25 Reference to any prior art in this specification is not, and should not be taken as, an acknowledgment or any form of suggestion that this prior art forms part of the general knowledge in any country.

Cancer represents one of the most debilitating diseases of our time.

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The financial cost of treating cancer and screening for and testing potential anti-cancer agents runs into billions of U.S. dollars. This cost is in addition to the personal costs of individuals, their families and in lost work productivity. The National Cancer Institute, for example, estimates overall annual costs for cancer in the U.S. to be about US\$107 billion.

- 5 This cost includes US\$37 billion for direct medical costs, US\$11 billion for morbidity costs (cost of lost productivity) and US\$59 billion for mortality costs.

Cancer is a complex group of more than 100 disease conditions. Although each type of cancer has certain characteristics unique to the cancer, every cancer does involve an

- 10 aberration in the body's own cells. Healthy cells that make up the body's tissues grow, divide and replace themselves or are replaced in an orderly way. This process keeps the body in good repair. Sometimes, however, normal cells lose their ability to limit and direct their growth. They divide too often and grow without any order. Too much tissue is produced and tumors begin to form.

15.

Hyaluronan (HA) is synthesised by a family of distinct yet related transmembrane proteins termed hyaluronan synthase (HAS) isoforms HAS1, 2 and 3, which can be distinguished from one another with respect to temporal and differential expression during mouse embryogenesis and in mature tissues, respectively and also in molecular weight of the HA

- 20 produced. The extracellular matrix polysaccharide HA or its acidic form, hyaluronic acid, is a linear, high molecular weight polymer comprised of repeating disaccharide units of ( $\beta$ 1-3) D-glucuronate-( $\beta$ 1-4)*N*-acetyl-D-glucosamine (Weissman & Meyer, *J. Am. Chem. Soc.* 76: 1753, 1954).

- 25 In accordance with the present invention, the level of each HAS isoform is selectively elevated or reduced to examine their individual role in cell behaviour.

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## SUMMARY OF THE INVENTION

Throughout the specification, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element or integer or group of elements or integers but not to the exclusion of any other element or integer or group of elements or integers.

- 5      inclusion of a stated element or integer or group of elements or integers but not to the exclusion of any other element or integer or group of elements or integers.

Nucleotide and amino acid sequences are referred to by a sequence identifier number (SEQ ID NO:). The SEQ ID NOs: correspond numerically to the sequence identifiers <400>1  
10     (SEQ ID NO:1), <400>2 (SEQ ID NO:2), etc. A summary of the sequence identifier numbers is provided in Table 1. A sequence listing is provided after the claims.

The present invention is directed to compounds, especially nucleic acid and nucleic acid-like oligomers or complexes comprising same, which are targeted to a nucleic acid  
15     encoding hyaluronan synthase (HAS) or a nucleic acid molecule required for or which facilitates expression of HAS-encoding material. In a preferred embodiment, the nucleic acid and nucleic acid-like oligomers or complexes comprising same, which are targeted to a nucleic acid encoding an isoform of HAS such as HAS1, HAS2 and/or HAS3. Pharmaceutical and other compositions comprising the compounds of the subject invention  
20     are also provided. Methods of screening for modulators of HAS gene expression in cells, tissues or animals are also contemplated. Methods of treating an animal, particularly a human, suspected of having or being prone to a disease or condition associated with HA levels or HAS gene expression are also set forth herein. Such methods comprise administering a therapeutically or prophylactically effective amount of one or more of the  
25     compounds or compositions of the present invention to the subject of need of treatment or suspected of needing prophylactic treatment.

The present invention provides, therefore, anti-sense, sense, siRNA, RNAi, ribozymes and DNAzymes which selectively reduce directly or indirectly, HAS gene expression.

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## BRIEF DESCRIPTION OF THE FIGURES

**Figure 1** is a graphical and photographic representation of Real time RT-PCR quantitation of mRNA expression of the HAS family and immunodetection of HAS2 in parental MDA-MB 231 and antisense transfectants. A: Expression and quantification of mRNA for HAS2 in parental MDA-MB 231, mock (pCIneo vector only) and stable clones of MDA MB-231 expressing antisense mRNA to HAS2 (ASHAS2). B: Expression and quantification of HAS1 and HAS3 in parental, mock and ASHAS2 transfectants.

5 C: Immunodetection of HAS2 protein on parental MDA-MB 231 and, D: on stable clones expressing antisense mRNA to HAS2. Photographs of parental and ASHAS2 transfectants at 400 $\times$  magnification. In parental cells note the periphery of the cell stains positively for the HAS2 epitope (arrows) that is absent in the antisense transfected, Panel D. E and F: Immunoreactivity of parental MDA MB231 to CD44 (panel E) and antisense transfected MDA-MB 231 (Panel F). Note the complete lack of staining in the antisense 15 transfected cells.

**Figure 2** is a graphical representation of the characterization of the molecular weigh of HA synthesised and differential expression of the hyaluronidase genes by parental, mock and HAS2 antisense transfected MDA-MB 231. A: Cells were seeded at  $7.5 \times 10^5$  cells in 75cm<sup>2</sup> culture flasks and grown for 24h in complete medium supplemented with 5 $\mu$ Ci of D-[6-<sup>3</sup>H]-glucosamine hydrochloride. To determine the MW of <sup>3</sup>H-HA in the medium, samples were subjected to size exclusion chromatography on a Sephadex S-1000 SF eluted in 0.15M NaCl/phosphate pH 7.25 at 13.6ml/h. This figure demonstrates the differences in molecular weight synthesized by parental MDA-MD 231 and their transfected counterparts harbouring antisense mRNA to HAS2. B: Total RNA extracted from parental, mock and ASHAS2 transfected MDA-MD 231 was analysed by RT-PCR to detect the levels of the hyaluronidase genes, notable HYAL-1, 2 and 3. PCR products were resolved by agarose gel electrophoresis containing ethidium bromide. Stained gels were then subjected to densitometric analysis to allow comparison of levels for each HYAL gene between 20 parental, mock and ASHAS2 transfected cells. Note, both parental and mock-transfected MDA-MD 231 cells express comparable levels of both HYAL-1 and 2 but do not express

HYAL-2. In contrast ASHAS2 transfected cells, HYAL-2 is not expressed whereas HYAL-3 was detected and HYAL-1 was moderately increased in expression.

- Figure 3 is a graphical representation of the quantification and comparison HAS in 5 parental, mock and ASHAS2 transfected MDA-MB 231. Cells were seeded at  $2.5 \times 10^5$ /cells in 25cm<sup>2</sup> culture flasks and incubated at 37°C for 24h, 48h, 72h, 96h, 120h and 144h. At each time points cells were trypsinized and counted using an automated coulter counter. HA concentration in the harvested culture medium was determined using a hyaluronic acid binding protein (HABP) assay, with the standards and reaction buffer 10 provided Corgenix Inc (Colorado, USA). HA synthesis by parental and mock transfected MDA-MB 231 was comparable over the duration of the experiment. In contrast, HA synthesis was significantly increased in ASHAS2 transfectants, where approximately 2- to 7-fold more HA was liberated into the culture medium.
- 15 Figure 4 is a graphical representation showing characterisation of cell proliferation in parental, mock and ASHAS2 transfected MDA MB 231. Parental, mock and ASHAS2 transfectants were harvested at approximately 80% confluency and seeded in to 24-well plates at a cell density of  $5 \times 10^3$ cells/well. The rate of cell growth was then followed for 24, 48, 72, and 96hours after plating. All cell counts were determined using an automated 20 Coulter counter. Whereas both parental and mock transfected MDA-MB 231 displayed exponential cell growth until 72 hours where cells became confluent, the ASHAS2 transfected cells grew at a much slower rate with an approximate 'lag' period in cell doubling of 24hours.
- 25 Figure 5 is a graphical representation of the effect of antisense inhibition of HAS2 on cell cycle. The transfected and control cells were seeded at  $2 \times 10^5$  cells/25cm<sup>2</sup> flask in the presence of 2mM thymidine and grown until 50% confluent. Cells were washed then returned to normal culture medium and harvested, by trypsinisation, at the following time points; 0h, 4h, 8h, 12h, 16h, 20h, 24h, 28h, 32h, and 36h then fixed in 95% w/v ethanol for 30 30 2h at 4°C Cells were pretreated with 100µg/mL RNAase (Sigma) and 50µg/ml propidium iodide (Sigma) for 30minutes at 37°C before determining the cell cycle stage in a FACS-

Calibur (Trade Mark) analytical instrument (Becton Dickinson, San Jose, CA). Panel A: population of cells in G<sub>0</sub>/G1; Panel B: in S phase, and PANEL C: in G<sub>2</sub>/M phase. Note the delay of 24 hours of entry into S PHASE in the ASHAS2 MDA MB 231 transfectants.

- 5 **Figure 6** is the graphical representation of the effect of HAS2 inhibition on the migratory behaviour of the highly metastatic MDA MD 231 cell line. The migration rate of parental, mock and antisense transfected cells was examined using the Boyden chamber chemoattraction assay as described in materials and methods. Whereas parental and mock transfectants displayed 100% migration, cells harbouring antisense to HAS2 were inhibited  
10 in migration by 93%.

Figure 7 is the graphical representation of the effect of antisense HAS2 inhibition on the tumorigenicity and metastasis of MDA MB 231. A: Parental; mock and ASHAS2 transfectants were inoculated into the mammary fat pad of nude mice. Primary tumor  
15 growth was followed over a 12 week period following implantation after which the extent of metastasis to other organs detected using Alu PCR. Mice inoculated with parental or mock transfected MDA MB 231 readily established primary tumors which were comparable in growth over the duration of the 12 week experiment. Mice inoculated with parental or mock transfected MDA MB 231 readily established primary tumors which  
20 were comparable in growth over the duration of the 12 week experiment. In contrast, however, mice inoculated with ASHAS2 transfectants did not establish primary tumors. B: Soft organ metastasis in mice inoculated with parental, mock and antisense transfected MDA MD 231. As assessed by Alu PCR, metastasis was most prevalent in brain, and lung but was also detected in kidneys and the liver in samples prepared from mice injected with  
25 either parental or mock transfectant MDA-MD 231 cells. No metastasis could be found in the aforementioned organs in mice that were injected with ASHAS2 transfectants.

## DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention employs compounds, preferably nucleotides and similar species for use in modulating the function or effect of nucleic acid molecules encoding hyaluronan synthase (HAS) and, in a particular embodiment, HAS1, HAS2 and/or HAS3 or of nucleic acid molecules required for or which facilitate expression of HAS (e.g. a promoter region). Preferably, the compounds of the present invention down regulate expression of HAS genetic material. This is accomplished by providing oligonucleotides which specifically hybridize or otherwise interact with one or more nucleic acid molecules encoding HAS or a nucleic acid molecule required for or which facilitates HAS gene expression. As used herein, the terms "nucleic acid" and "nucleic acid molecule encoding HAS" have been used for convenience to encompass DNA encoding HAS, RNA (including pre-mRNA and mRNA or portions thereof) transcribed from such DNA, and also cDNA derived from such RNA. The hybridization or interaction of a compound of the present invention with a target nucleic acid may encompass antisense or sense targeting. The latter is referred to herein as sense suppression. Consequently, the present invention provides for antisense or sense inhibition. Such antisense or sense inhibition is typically based upon hydrogen bonding-based hybridization of oligonucleotide strands or segments such that at least one strand or segment is cleaved, degraded, or otherwise rendered inoperable. Alternatively, post-transcriptional gene silencing (PTGS) may be achieved using sense suppression (formally known as co-suppression). In yet another alternative, complexes comprising nucleic acid molecules and proteins (e.g. ribonucleases) such as RNAi, ribozymes and DNAzymes may be employed.

The target nucleic acid molecules include the HAS coding sequences, a promoter region, a 3' regulatory region or a nucleotide sequence, the expression of which, facilitates or inhibits HAS gene expression (e.g. a regulatory gene, activator gene or reporter gene).

As used herein, reference to HAS includes any molecule with the same function. In a preferred aspect, reference to "HAS", includes reference to the isoforms HAS1, HAS2 or HAS3. In a particularly preferred embodiment, the HAS is HAS2.

The functions of the nucleic acid molecule to be down regulated include replication, transcription and/or translation. Where the nucleic acid molecule is RNA, the compounds may target translocation of the RNA to a site of protein translation, translocation of the

5 RNA to sites within the cell which are distant from the site of RNA synthesis, translation of protein from the RNA, splicing of the RNA to yield one or more RNA species, and catalytic activity or complex formation involving the RNA which may be engaged in or facilitated by the RNA. One preferred result of such interference with target nucleic acid function is reduction in the level of expression of HAS. Inhibition is the preferred form of

10 modulation of expression and mRNA is the preferred target nucleic acid.

In the context of this invention, "hybridization" means the pairing of complementary strands of nucleic acids. In the present invention, the preferred mechanism of pairing involves hydrogen bonding, which may be Watson-Crick, Hoogsteen or reversed

15 Hoogsteen hydrogen bonding, between complementary nucleoside or nucleotide bases (nucleotides) of the strands of oligomeric compounds. For example, adenine and thymine are complementary nucleotides which pair through the formation of hydrogen bonds. Hybridization can occur under varying circumstances.

20 An antisense or sense compound is specifically hybridizable when binding of the compound to the target nucleic acid interferes with the normal function of the target nucleic acid to cause a loss of activity, and there is a sufficient degree of complementarity to avoid non-specific binding of the antisense or sense compound to non-target nucleic acid sequences under conditions in which specific binding is desired, i.e., under

25 physiological conditions in the case of *in vivo* assays or therapeutic treatment, and under conditions in which assays are performed in the case of *in vitro* assays.

A sense compound includes RNAi or other complex which includes PTGS.

30 In the present invention the phrase "stringent hybridization conditions" or "stringent conditions" refers to conditions under which a compound of the invention will hybridize to

its target sequence, but to a minimal number of other sequences. Stringent conditions are sequence-dependent and will be different in different circumstances and in the context of this invention, "stringent conditions" under which oligomeric compounds hybridize to a target sequence are determined by the nature and composition of the oligomeric  
5 compounds and the assays in which they are being investigated.

"Complementary," as used herein, refers to the capacity for precise pairing between two nucleotides of an oligomeric compound. For example, if a nucleotide at a certain position of an oligonucleotide (an oligomeric compound), is capable of hydrogen bonding with a  
10 nucleotide at a certain position of a target nucleic acid, said target nucleic acid being a DNA, RNA, or oligonucleotide molecule, then the position of hydrogen bonding between the oligonucleotide and the target nucleic acid is considered to be a complementary position. The oligonucleotide and the further DNA, RNA, or oligonucleotide molecule are complementary to each other when a sufficient number of complementary positions in  
15 each molecule are occupied by nucleotides which can hydrogen bond with each other. Thus, "specifically hybridizable" and "complementary" are terms which are used to indicate a sufficient degree of precise pairing or complementarity over a sufficient number of nucleotides such that stable and specific binding occurs between the oligonucleotide and a target nucleic acid.  
20

It is understood in the art that the sequence of an antisense or sense compound need not be 100% complementary to that of its target nucleic acid to be specifically hybridizable. Moreover, an oligonucleotide may hybridize over one or more segments such that intervening or adjacent segments are not involved in the hybridization event (e.g., a loop  
25 structure or hairpin structure). It is preferred that the antisense or sense compounds of the present invention comprise at least 70% sequence complementarity to a target region within the target nucleic acid, such as 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 or 100% complementarity to the nucleic acid sequence to which they are targeted. For example, an antisense or sense  
30 compound in which 18 out of 20 nucleotides of the antisense or sense compound are complementary to a target region, and would therefore specifically hybridize, would

- 10 -

represent 90 percent complementarity. In this example, the remaining noncomplementary nucleotides may be clustered or interspersed with complementary nucleotides and need not be contiguous to each other or to complementary nucleotides. As such, an antisense or sense compound which is 18 nucleotides in length having 4 (four) noncomplementary  
5 nucleotides which are flanked by two regions of complete complementarity with the target nucleic acid would have 77.8% overall complementarity with the target nucleic acid and would thus fall within the scope of the present invention. Percent complementarity of an antisense or sense compound with a region of a target nucleic acid can be determined routinely using BLAST programs (basic local alignment search tools) and PowerBLAST  
10 programs known in the art (Altschul et al., *J. Mol. Biol.* 215: 403-410, 1990; Zhang and Madden, *Genome Res.* 7: 649-656, 1997).

According to the present invention, compounds include antisense or sense nucleic acids, antisense or sense oligomeric compounds, antisense or sense oligonucleotides, ribozymes,  
15 sense oligonucleotides, full-length sense molecules, external guide sequence (EGS) oligonucleotides, alternate splicers, primers, probes, and other oligomeric compounds which hybridize to at least a portion of the target nucleic acid. As such, these compounds may be introduced in the form of single-stranded, double-stranded, circular or hairpin oligomeric compounds and may contain structural elements such as internal or terminal  
20 bulges or loops. Once introduced to a system, the compounds of the invention may elicit the action of one or more enzymes or structural proteins to effect modification of the target nucleic acid.

As used herein, an "antisense" or "sense" molecule includes an RNA molecule which, by  
25 binding to a complementary sequence in either RNA or DNA, inhibits the function and/or completion of synthesis of the latter molecule. It is involved in various regulatory systems in vivo. Artificial antisense or sense RNAs have been used to inhibit translation of specific mRNA molecules both in living cells (eukaryotic and bacterial) and in cell-free systems.

30 One non-limiting example of such an enzyme is RNase H, a cellular endonuclease which cleaves the RNA strand of an RNA:DNA duplex. It is known in the art that single-

stranded antisense or sense compounds which are "DNA-like" elicit RNase H. Activation of RNase H, therefore, results in cleavage of the RNA target, thereby greatly enhancing the efficiency of oligonucleotide-mediated inhibition of gene expression. Similar roles have been postulated for other ribonucleases such as those in the RNase III and ribonuclease L  
5 family of enzymes.

While the preferred form of antisense or sense compounds are single-stranded oligonucleotides, in many species the introduction of double-stranded structures, such as double-stranded RNA (dsRNA) molecules, miRNAs, short-interfering RNA molecules  
10 (siRNA) and full-length dsRNAs.

Small interfering RNAs (siRNAs) have an integral role in the phenomenon of RNA interference (RNAi). In RNAi, dsRNAs introduced into certain organisms or cells are degraded into approximately 22 nucleotide fragments. These 22 nucleotide siRNA  
15 molecules then bind to the complementary portion of their target mRNA and tag it for degradation.

A second class of regulatory small RNAs contemplated by the present invention are referred to as small temporal RNAs. Approximately 22 nucleotide *lin-4* and *let-7* RNAs  
20 are example of this group. These RNA molecules have a role in temporal regulation of *C. elegans* development. These are initially processed from an approximate 70 nucleotide ssRNA transcript folded into a stem loop structure. After processing, these stRNAs are thought to prevent translation of their target mRNAs by binding to the targets complementary 3' untranslated regions (UTRs). Dicer, RNAase enzyme processes both the  
25 types of RNAs (Grishok *et al.* *Science* 287(5462):2494-2497, 2000).

In the context of this invention, the term "oligomeric compound" refers to a polymer or oligomer comprising a plurality of monomeric units. In the context of this invention, the term "oligonucleotide" refers to an oligomer or polymer of ribonucleic acid (RNA) or  
30 deoxyribonucleic acid (DNA) or mimetics, chimeras, analogs and homologs thereof. This term includes oligonucleotides composed of naturally occurring nucleotides, sugars and

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covalent internucleoside (backbone) linkages as well as oligonucleotides having non-naturally occurring portions which function similarly. Such modified or substituted oligonucleotides are often preferred over native forms because of desirable properties such as, for example, enhanced cellular uptake, enhanced affinity for a target nucleic acid and

5 increased stability in the presence of nucleases.

While oligonucleotides are a preferred form of the compounds of this invention, the present invention comprehends other families of compounds as well, including but not limited to oligonucleotide analogs and mimetics such as those herein described.

10

The compounds in accordance with this invention preferably comprise from about 10 to about 2000 nucleotides (i.e. from about 10 to about 2000 linked nucleosides). One of ordinary skill in the art will appreciate that the invention embodies compounds of 10, 11,

12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35,

15 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59,

60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 90, 100,

110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280,

290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460,

470, 480, 490, 500, 510, 520, 530, 540, 550, 560, 570, 580, 590, 600, 610, 620, 630, 640,

20 650, 660, 670, 680, 690, 700, 710, 720, 730, 740, 750, 760, 770, 780, 790, 800, 810, 820,

830, 840, 850, 860, 870, 880, 890, 900, 910, 920, 930, 940, 950, 960, 970, 980, 990, 1000,

1010, 1020, 1030, 1040, 1050, 1060, 1080, 1090, 1100, 1110, 1120, 1130, 1140, 1150,

1160, 1170, 1180, 1190, 1200, 1210, 1220, 1230, 1240, 1250, 1260, 1270, 1280, 1290,

1300, 1310, 1320, 1330, 1340, 1350, 1360, 1370, 1380, 1390, 1400, 1410, 1420, 1430,

25 1440, 1450, 1460, 1470, 1480, 1490, 1500, 1510, 1520, 1530, 1540, 1550, 1560, 1570,

1580, 1590, 1600, 1610, 1620, 1630, 1640, 1650, 1660, 1670, 1680, 1690, 1700, 1710,

1720, 1730, 1740, 1750, 1760, 1770, 1780, 1790, 1800, 1810, 1820, 1830, 1840, 1850,

1860, 1870, 1880, 1890, 1900, 1910, 1920, 1930, 1940, 1950, 1960, 1970, 1980, 1990 or

2000 nucleotides in length.

30

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Antisense or sense compounds 10-2000 nucleotides in length comprising a stretch of at least ten (10) such as 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 consecutive nucleotides selected from within the illustrative antisense or sense compounds are considered to be suitable antisense or sense compounds as well.

5

Exemplary preferred antisense or sense compounds include oligonucleotide sequences that comprise at least the 10 consecutive nucleotides from the 5'-terminus of one of the illustrative preferred antisense or sense compounds (the remaining nucleotides being a consecutive stretch of the same oligonucleotide beginning immediately upstream of the 5'-

- 10 terminus of the antisense or sense compound which is specifically hybridizable to the target nucleic acid and continuing until the oligonucleotide contains about 10 to about 2000 nucleotides). Similarly preferred antisense or sense compounds are represented by oligonucleotide sequences that comprise at least the 10 consecutive nucleotides from the 3'-terminus of one of the illustrative preferred antisense or sense compounds (the
- 15 remaining nucleotides being a consecutive stretch of the same oligonucleotide beginning immediately downstream of the 3'-terminus of the antisense or sense compound which is specifically hybridizable to the target nucleic acid and continuing until the oligonucleotide contains about 10 to about 2000 nucleotides). One having skill in the art armed with the preferred antisense or sense compounds illustrated herein will be able, without undue
- 20 experimentation, to identify further preferred antisense or sense compounds.

Candidate compounds are also referred to herein as "lead" compounds. In the present invention, the target nucleic acid encodes HAS or is a gene required for HAS gene expression. As indicated above, the term "HAS" includes isoforms HAS1, HAS2 and

25 HAS3.

- 30 The targeting process usually also includes determination of at least one target region, segment, or site within the target nucleic acid for the antisense or sense interaction to occur such that the desired effect, e.g., to reduce expression, will result. Within the context of the present invention, the term "region" is defined as a portion of the target nucleic acid having at least one identifiable structure, function, or characteristic. Within regions of

target nucleic acids are segments. "Segments" are defined as smaller or sub-portions of regions within a target nucleic acid. "Sites," as used in the present invention, are defined as positions within a target nucleic acid.

- 5 Since, as is known in the art, the translation initiation codon is typically 5'-AUG (in transcribed mRNA molecules; 5'-ATG in the corresponding DNA molecule), the translation initiation codon is also referred to as the "AUG codon," the "start codon" or the "AUG start codon". A minority of genes have a translation initiation codon having the RNA sequence 5'-GUG, 5'-UUG or 5'-CUG, and 5'-AUA, 5'-ACG and 5'-CUG have been
- 10 shown to function *in vivo*. Thus, the terms "translation initiation codon" and "start codon" can encompass many codon sequences, even though the initiator amino acid in each instance is typically methionine (in eukaryotes). It is also known in the art that eukaryotic genes may have two or more alternative start codons, any one of which may be preferentially utilized for translation initiation in a particular cell type or tissue, or under a
- 15 particular set of conditions. In the context of the invention, "start codon" and "translation initiation codon" refer to the codon or codons that are used *in vivo* to initiate translation of an mRNA transcribed from a gene encoding HAS, regardless of the sequence(s) of such codons. It is also known in the art that a translation termination codon (or "stop codon") of a gene may have one of three sequences, i.e., 5'-UAA, 5'-UAG and 5'-UGA (the
- 20 corresponding DNA sequences are 5'-TAA, 5'-TAG and 5'-TGA, respectively).

- The terms "start codon region" and "translation initiation codon region" refer to a portion of such an mRNA or gene that encompasses from about 25 to about 50 contiguous nucleotides in either direction (i.e., 5' or 3') from a translation initiation codon. Similarly, the terms "stop codon region" and "translation termination codon region" refer to a portion of such an mRNA or gene that encompasses from about 25 to about 50 contiguous nucleotides in either direction (i.e., 5' or 3') from a translation termination codon. Consequently, the "start codon region" (or "translation initiation codon region") and the "stop codon region" (or "translation termination codon region") are all regions which may
- 25 be targeted effectively with the antisense or sense compounds of the present invention.
  - 30

- 15 -

The open reading frame (ORF) or "coding region," which is known in the art to refer to the region between the translation initiation codon and the translation termination codon, is also a region which may be targeted effectively. Within the context of the present invention, a preferred region is the intragenic region encompassing the translation initiation or termination codon of the open reading frame (ORF) of a gene.

Other target regions include the 5' untranslated region (5'UTR), known in the art to refer to the portion of an mRNA in the 5' direction from the translation initiation codon, and thus including nucleotides between the 5' cap site and the translation initiation codon of an mRNA (or corresponding nucleotides on the gene), and the 3' untranslated region (3'UTR), known in the art to refer to the portion of an mRNA in the 3' direction from the translation termination codon, and thus including nucleotides between the translation termination codon and 3' end of an mRNA (or corresponding nucleotides on the gene). The 5' cap site of an mRNA comprises an N7-methylated guanosine residue joined to the 5'-most residue of the mRNA *via* a 5'-5' triphosphate linkage. The 5' cap region of an mRNA is considered to include the 5' cap structure itself as well as the first 50 nucleotides adjacent to the cap site. It is also preferred to target the 5' cap region.

Although some eukaryotic mRNA transcripts are directly translated, many contain one or more regions, known as "introns," which are excised from a transcript before it is translated. The remaining (and therefore translated) regions are known as "exons" and are spliced together to form a continuous mRNA sequence. Targeting splice sites, i.e., intron-exon junctions or exon-intron junctions, may also be particularly useful in situations where aberrant splicing is implicated in disease, or where an overproduction of a particular splice product is implicated in disease. Aberrant fusion junctions due to rearrangements or deletions are also preferred target sites. mRNA transcripts produced via the process of splicing of two (or more) mRNAs from different gene sources are known as "fusion transcripts". It is also known that introns can be effectively targeted using antisense or sense compounds targeted to, for example, DNA or pre-mRNA.

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It is also known in the art that alternative RNA transcripts can be produced from the same genomic region of DNA. These alternative transcripts are generally known as "variants". More specifically, "pre-mRNA variants" are transcripts produced from the same genomic DNA that differ from other transcripts produced from the same genomic DNA in either  
5 their start or stop position and contain both intronic and exonic sequence.

Upon excision of one or more exon or intron regions, or portions thereof during splicing, pre-mRNA variants produce smaller "mRNA variants". Consequently, mRNA variants are processed pre-mRNA variants and each unique pre-mRNA variant must always produce a  
10 unique mRNA variant as a result of splicing. These mRNA variants are also known as "alternative splice variants". If no splicing of the pre-mRNA variant occurs then the pre-mRNA variant is identical to the mRNA variant.

It is also known in the art that variants can be produced through the use of alternative  
15 signals to start or stop transcription and that pre-mRNAs and mRNAs can possess more than one start codon or stop codon. Variants that originate from a pre-mRNA or mRNA that use alternative start codons are known as "alternative start variants" of that pre-mRNA or mRNA. Those transcripts that use an alternative stop codon are known as "alternative stop variants" of that pre-mRNA or mRNA. One specific type of alternative stop variant is  
20 the "polyA variant" in which the multiple transcripts produced result from the alternative selection of one of the "polyA stop signals" by the transcription machinery, thereby producing transcripts that terminate at unique polyA sites. Within the context of the invention, the types of variants described herein are also preferred target nucleic acids.

25 The locations on the target nucleic acid to which the preferred antisense or sense compounds hybridize are hereinbelow referred to as "preferred target segments." As used herein the term "preferred target segment" is defined as at least a 10-nucleotide portion of a target region to which an active antisense or sense compound is targeted. While not wishing to be bound by theory, it is presently believed that these target segments represent  
30 portions of the target nucleic acid which are accessible for hybridization.

- 17 -

While the specific sequences of certain preferred target segments are set forth herein, one of skill in the art will recognize that these serve to illustrate and describe particular embodiments within the scope of the present invention. Additional preferred target segments may be identified by one having ordinary skill.

- 5 Target segments 10-2000 nucleotides in length comprising a stretch of at least ten (10) consecutive nucleotides selected from within the illustrative preferred target segments are considered to be suitable for targeting as well.
- 10 Target segments can include DNA or RNA sequences that comprise at least the 8 consecutive nucleotides from the 5'-terminus of one of the illustrative preferred target segments (the remaining nucleotides being a consecutive stretch of the same DNA or RNA beginning immediately upstream of the 5'-terminus of the target segment and continuing until the DNA or RNA contains about 10 to about 2000 nucleotides). Similarly preferred  
15 target segments are represented by DNA or RNA sequences that comprise at least the 10 consecutive nucleotides from the 3'-terminus of one of the illustrative preferred target segments (the remaining nucleotides being a consecutive stretch of the same DNA or RNA beginning immediately downstream of the 3'-terminus of the target segment and continuing until the DNA or RNA contains about 10 to about 2000 nucleotides). One  
20 having skill in the art armed with the preferred target segments illustrated herein will be able, without undue experimentation, to identify further preferred target segments.

Once one or more target regions, segments or sites have been identified, antisense or sense compounds are chosen which are sufficiently complementary to the target, i.e., hybridize  
25 sufficiently well and with sufficient specificity, to give the desired effect, i.e. to reduce HAS gene expression or levels of HAS.

In a further embodiment, the "preferred target segments" identified herein may be employed in a screen for additional compounds that modulate the expression of the HAS  
30 gene. "Modulators" are those compounds that decrease or increase the expression of a nucleic acid molecule encoding HAS and which comprise at least a 10-nucleotide portion

which is complementary to a preferred target segment. The screening method comprises the steps of contacting a preferred target segment of a nucleic acid molecule encoding HAS with one or more candidate modulators, and selecting for one or more candidate modulators which decrease or increase the expression of a nucleic acid molecule encoding HAS. Once it is shown that the candidate modulator or modulators are capable of modulating (e.g. either decreasing or increasing) the expression of a nucleic acid molecule encoding HAS, the modulator may then be employed in further investigative studies of the function of HAS, or for use as a research, diagnostic, or therapeutic agent in accordance with the present invention.

10

The preferred target segments of the present invention may be also be combined with their respective complementary antisense or sense compounds of the present invention to form stabilized double-stranded (duplexed) oligonucleotides:

15 Such double stranded oligonucleotide moieties have been shown in the art to modulate target expression and regulate translation as well as RNA processing via an antisense or sense mechanism. Moreover, the double-stranded moieties may be subject to chemical modifications (Fire *et al.*, *Nature* 391: 806-811, 1998; Timmons and Fire, *Nature* 395: 854, 1998; Timmons *et al.*, *Gene* 263: 103-112, 2001; Tabara *et al.*, *Science* 282: 430-431, 20

20 Montgomery *et al.*, 1998, *supra*; Tuschl *et al.*, *Genes Dev.* 13: 3191-3197, 1999; Elbashir *et al.*, *Nature*, 411: 494-498, 2001; Elbashir *et al.*, *Genes Dev.* 15: 188-200, 2001). For example, such double-stranded moieties have been shown to inhibit the target by the classical hybridization of antisense or sense strand of the duplex to the target, thereby triggering enzymatic degradation of the target (Tijsterman *et al.*, 2002, *supra*).

25

The compounds of the present invention can also be applied in the areas of drug discovery and target validation. The present invention comprehends the use of the compounds and preferred target segments identified herein in drug discovery efforts to elucidate relationships that exist between HA, HAS or HA/HAS interaction and a disease state, phenotype, or condition. These methods include detecting or modulating HAS comprising contacting a sample, tissue, cell, or organism with the compounds of the present invention,

measuring the nucleic acid or protein level of HAS and/or a related phenotypic or chemical endpoint at some time after treatment, and optionally comparing the measured value to a non-treated sample or sample treated with a further compound of the invention. These methods can also be performed in parallel or in combination with other experiments to

5 determine the function of unknown genes for the process of target validation or to determine the validity of a particular gene product as a target for treatment or prevention of a particular disease, condition, or phenotype.

The present invention contemplates the use of therapeutic agents to treat subjects suffering  
10 from diseases and disorders associated with HA. Subjects treated using the compositions and compounds of the present invention include any animal who may benefit from such treatment. These include, without limitation, humans, marmosets, orangutans and gorillas, livestock animals (e.g. cows, sheep, pigs, horses, donkeys), laboratory test animals (e.g. mice, rats, guinea pigs, hamsters, rabbits), companion animals (e.g. cats, dogs) and  
15 captured wild animals (e.g. rodents, foxes, deer, kangaroos. A particularly preferred host is a human, primate or livestock animal.

The compounds of the present invention can be utilized for diagnostics, therapeutics, prophylaxis and as research reagents and kits. Furthermore, antisense or sense  
20 oligonucleotides, which are able to inhibit gene expression with exquisite specificity, are often used by those of ordinary skill to elucidate the function of particular genes or to distinguish between functions of various members of a biological pathway.

For use in kits and diagnostics, the compounds of the present invention, either alone or in  
25 combination with other compounds or therapeutics, can be used as tools in differential and/or combinatorial analyses to elucidate expression patterns of a portion or the entire complement of genes expressed within cells and tissues.

As one non-limiting example, expression patterns within cells or tissues treated with one or  
30 more antisense or sense compounds are compared to control cells or tissues not treated with antisense or sense compounds and the patterns produced are analyzed for differential

levels of gene expression as they pertain, for example, to disease association, signalling pathway, cellular localization, expression level, size, structure or function of the genes examined. These analyses can be performed on stimulated or unstimulated cells and in the presence or absence of other compounds which affect expression patterns.

5

Examples of methods of gene expression analysis known in the art include DNA arrays or microarrays (Brazma and Vilo, *FEBS Lett.* 480: 17-24, 2000; Celis *et al.*, *FEBS Lett.* 480: 2-16, 2000), SAGE (serial analysis of gene expression)(Madden *et al.*, *Drug Discov. Today* 5: 415-425, 2000), READS (restriction enzyme amplification of digested cDNAs) (Prashar

10 and Weissman, *Methods Enzymol.* 303: 258-272, 1999), TOGA (total gene expression analysis) (Sutcliffe *et al.*, *Proc. Natl. Acad. Sci. USA* 97: 1976-1981, 2000), protein arrays and proteomics (Celis *et al.* 2000, *supra*; Jungblut *et al.*, *Electrophoresis* 20: 2100-2110, 1999), expressed sequence tag (EST) sequencing (Celis *et al.*, 2000, *supra*; Larsson *et al.*,

15 *J. Biotechnol.* 80: 143-157, 2000), subtractive RNA fingerprinting (SuRF) (Fuchs *et al.*, *Anal. Biochem.* 286: 91-98, 2000; Larson *et al.*, *Cytometry* 41: 203-208, 2000), subtractive cloning, differential display (DD) (Jurecic and Belmont, *Curr. Opin. Microbiol.* 3: 316-321, 2000), comparative genomic hybridization (Carulli *et al.*, *J. Cell Biochem. Suppl.* 31: 286-296, 1998), FISH (fluorescent *in situ* hybridization) techniques (Going and Gusterson, *Eur. J. Cancer*, 35: 1895-1904, 1999) and mass spectrometry methods (To, *Comb. Chem. High Throughput Screen*, 3: 235-241, 2000).

The compounds of the invention are useful for research and diagnostics, because these compounds hybridize to nucleic acids encoding HAS. For example, oligonucleotides that are shown to hybridize with such efficiency and under such conditions as disclosed herein  
25 as to be effective HAS inhibitors of HAS gene expression inhibitors will also be effective primers or probes under conditions favoring gene amplification or detection, respectively. These primers and probes are useful in methods requiring the specific detection of nucleic acid molecules encoding HAS and in the amplification of said nucleic acid molecules for detection or for use in further studies of HAS or its gene. Hybridization of the antisense or  
30 sense oligonucleotides, particularly the primers and probes, of the invention with a nucleic acid encoding HAS can be detected by means known in the art. Such means may include

conjugation of an enzyme to the oligonucleotide, radiolabelling of the oligonucleotide or any other suitable detection means. Kits using such detection means for detecting the level of HAS in a sample may also be prepared.

- 5 The specificity and sensitivity of antisense or sense is also harnessed by those of skill in the art for therapeutic uses. Antisense or sense compounds have been employed as therapeutic moieties in the treatment of disease states in animals, including humans. Antisense or sense oligonucleotide drugs, including ribozymes, have been safely and effectively administered to humans and numerous clinical trials are presently underway. It  
10 10 is thus established that antisense or sense compounds can be useful therapeutic modalities that can be configured to be useful in treatment regimes for the treatment of cells, tissues and animals, especially humans.

For therapeutics, an animal, preferably a human, suspected of having a disease or disorder  
15 15 which can be treated by modulating the expression of the HAS gene is treated by administering antisense or sense compounds in accordance with this invention. For example, in one non-limiting embodiment, the methods comprise the step of administering to the animal in need of treatment, a therapeutically effective amount of an HAS gene expression inhibitor. The HAS gene expression inhibitors of the present invention  
20 20 effectively inhibit the activity of the HAS protein or inhibit the expression of the HAS gene. In one embodiment, the activity or expression of HAS or its gene in an animal is inhibited by about 10%. Preferably, the activity or expression of HAS or its gene in an animal is inhibited by about 30%. More preferably, the activity or expression of HAS or its gene in an animal is inhibited by 50% or more.

25

For example, the reduction of the expression of the HAS gene may be measured in serum, adipose tissue, skin cells, liver or any other body fluid, tissue or organ of the animal. Preferably, the cells contained within said fluids, tissues or organs being analyzed contain a nucleic acid molecule encoding an HAS protein.

30

The compositions and compounds of the present invention can be used in the treatment or prevention of diseases associated with HA. The present invention contemplates treatment of diseases and disorders such as A-Beta-Lipoproteinemia, A-V, A Beta-2-Microglobulin Amyloidosis, A-T, A1AD, A1AT, Aagenes, Aarskog syndrome, Aarskog-Scott Syndrome, Aase-smith syndrome, Aase Syndrome, AAT, Abderhalden-Kaufmann-Lignac Syndrome, Abdominal Muscle Deficiency Syndrome, Abdominal Wall Defect, Abdominal Epilepsy, Abdominal Migraine, Abductor Spasmodic Dysphonia, Abductor Spastic Dysphonia, Abercrombie Syndrome, blepharon-Macrostomia Syndrome, ABS, Absence of HPRT, Absence of Corpus Callosum Schinzel Typ, Absence Defect of Limbs Scalp and

5 Skull, Absence of Menstruation Primar, Absence of HGPRT, Absorptive Hyperoxaluriaor Enteric, Abt-Letterer-Siwe Disease, ACADL, ACADM Deficiency, ACADM, ACADS, Acanthocytosis-Neurologic Disorder, Acanthocytosis, Acantholysis Bullosa, Acanthosis Nigricans, Acanthosis Bullosa, Acanthosis Nigricans With Insulin Resistance Type A, Acanthosis Nigricans With Insulin Resistance Type B, Acanthotic Nevus, Acatalasemia,

10 15 Acatalasia, ACC, Accessory Atrioventricular Pathways, Accessory Atrioventricular Pathways, Acephaly, ACF with Cardiac Defects, Achalasia, Achard-Thiers Syndrome, ACHARD (Marfan variant), Achard's syndrome, Acholuric Jaundice, Achondrogenesis, Achondrogenesis Type IV, Achondrogenesis Type III, Achondroplasia, Achondroplasia Tarda, Achondroplastic Dwarfism, Achoo Syndromę, Achromat, Achromatope,

20 25 Achromatopic, Achromatopsia, Achromic Nevi, Acid Ceramidase Deficiency, Acid Maltase Deficiency, Acid Maltase Deficiency, Acid Beta-glucosidase Deficiency, Acidemia Methylmalonic, Acidemia Propionic, Acidemia with Episodic Ataxia and Weakness, Acidosis, Aclasis Tarsoepiphyseal, ACM, Acoustic Neurilemoma, Acoustic Neuroma, ACPS with Leg Hypoplasia, ACPS II, ACPS IV, ACPS III, Acquired Aphasia with Convulsive Disorder, Acquired Brown Syndrome, Acquired Epileptic Aphasia, Acquired Factor XIII Deficiency, Acquired Form of ACC (caused by infection while still in womb), Acquired Hyperoxaluria, Acquired Hypogammaglobulinemia, Acquired Immunodeficiency Syndrome (AIDS), Acquired Iron Overload, Acquired Lipodystrophy, Acquired Partial Lipodystrophy, Acquired Wandering Spleen, ACR, Acral Dysostosis with

30 Facial and Genital Abnormalities, Acro Renal, Acrocallosal Syndrome Schinzel Type, Acrocephalosyndactyly, Acrocephalosyndactyly Type I, Acrocephalosyndactyly Type I

- Subtype I, Acrocephalopolysyndactyly Type II, Acrocephalopolysyndactyly Type III, Acrocephalopolysyndactyly Type IV, Acrocephalopolysyndactyly V (ACS5 or ACS V)  
Subtype I, Acrocephaly, Skull Asymmetry and Mild Syndactyly, Acrocephaly, Acrochondrohyperplasia, Acrodermatitis Enteropathica, Acrodysostosis, Acrodystrophic
- 5 Neuropathy, Acrodystrophic Neuropathy, Acrofacial Dysostosis Nager Type, Acrofacial Dysostosis Nager Type, Acrofacial Dysostosis Postaxial Type, Acrofacial Dysostosis Type Genee-Wiedep, Acrogeria Familial, Acromegaly, Acromelalgia Hereditary, Acromesomelic Dysplasia, Acromesomelic Dwarfism, Acromicric Skeletal Dysplasia, Acromicric Dysplasia, Acroosteolysis with Osteoporosis and Changes in Skull and
- 10 Mandible, Acroosteolysis, Acroparesthesia, ACS I, ACS Type II, ACS Type III, ACS, ACS3, ACTH Deficiency, Action Myoclonus, Acute Brachial Neuritis Syndrome, Acute Brachial Radiculitis Syndrome, Acute Cerebral Gaucher Disease, Acute Cholangitis, Acute Disseminated Encephalomyeloradiculopathy, Acute Disseminated Histiocytosis-X, Acute Hemorrhagic Polioencephalitis, Acute Idiopathic Polyneuritis, Acute Immune-Mediation
- 15 Polyneuritis, Acute Infantile Pelizaeus-Merzbacher Brain Sclerosis, Acute Intermittant Porphyria, Acute Porphyrias, Acute Sarcoidosis, Acute Shoulder Neuritis, Acute Toxic Epidermolysis, Acyl-CoA Dehydrogenase Deficiency Long-Chain, Acyl-CoA Dehydrogenase Deficiency Short-Chain, Acyl-CoA Dihydroxyacetone Acyltransferase, Acyl-coenzyme A Oxidase Deficiency, ADA, ADA Deficiency, Adam Complex,
- 20 Adamantiades-Behcet's Syndrome, Adamantinoma, Adams Oliver Syndrome, Adaptive Colitis, ADD combined type, ADD, Addison Disease with Cerebral Sclerosis, Addison's Anemia, Addison's Anemia, Addison's Disease, Addison's Disease, Addison's Disease, Addison-Biermer Anemia, Addison-Biermer Anemia, Addison-Schilder Disease, Addisonian Pernicious Anemia, Addisonian Pernicious Anemia, Adducted Thumbs-Mental
- 25 Retardation, Adductor Spasmodic Dysphonia, Adductor Spastic Dysphonia, Adenoma Associated Virilism of Older Women, Adenomatosis of the Colon and Rectum, Adenomatous polyposis of the Colon, Adenomatous Polyposis Familial, Adenosine Deaminase Deficiency, Adenosine Deaminase Deficiency, Adenylosuccinase deficiency, ADHD predominantly hyperactive-impulsive type, ADHD predominantly inattentive type,
- 30 ADHD, Adhesive Arachnoiditis, Adie Syndrome, Adie's Syndrome, Adie's Tonic Pupil, Adie's Pupil, Adipogenital Retinitis Pigmentosa Polydactyly, Adipogenital-Retinitis

- Pigmentosa Syndrome, Adiposa Dolorosa, Adiposis Dolorosa, Adiposogenital Dystrophy, Adolescent Cystinosis, ADPKD, Adrenal Cortex Adenoma, Adrenal Disease, Adrenal Hyperfunction resulting from Pituitary ACTH Excess, Adrenal Hypoplasia, Adrenal Insufficiency, Adrenal Neoplasm, Adrenal Virilism, Adrenal Virilism, Adreno-Retinitis
- 5 Pigmentosa-Polydactyly Syndrome, Adrenocortical Insufficiency, Adrenocortical Hypofunction, Adrenocorticotropic Hormone Deficiency Isolated, Adrenogenital Syndrome, Adrenogenital Syndrome, Adrenoleukodystrophy, Adrenomyeloneuropathy, Adreno-Retinitis Pigmentosa-Polydactyly Syndrome, Adult Cystinosis, Adult Dermatomyositis, Adult Hypophosphatasia, Adult Macula Lutea Retinae Degeneration,
- 10 Adult Onset ALD, Adult-Onset Ceroidosis, Adult Onset Medullary Cystic Disease, Adult Onset Pernicious Anemia, Adult Onset Pernicious Anemia, Adult Onset Schindler Disease, Adult-Onset Subacute Necrotizing Encephalomyopathy, Adult Onset Pernicious Anemia, Adult Polycystic Kidney Disease, Adult Onset Medullary Cystic Disease, Adynlosuccinate Lyase Deficiency, AE, AEC Syndrome, AFD, AFD, Afibrinogenemia, African Siderosis,
- 15 AGA, Aganglionic Megacolon, Age Related Macular Degeneration, Agenesis of Commissura Magna Cerebri, Agenesis of Corpus Callosum, Agenesis of Corpus Callosum-Infantile Spasms-Ocular Anomalies, Agenesis of Corpus Callosum and Chorioretinal Abnormality, Agenesis of Corpus Callosum-Chorioretinitis Abnormality, Aggressive mastocytosis, Agnosis Primary, AGR Triad, AGU, Agyria, Agyria-pachygria-
- 20 band spectrum, AHC, AHD, AHDS, AHF Deficiency, AHG Deficiency, AHO, Ahumada Del Castillo, Aicardi Syndrome, Aicardi Syndrome, AIED, AIM, AIP, AIS, AIS, Akinetic Seizure, ALA-D Porphyria, Alactasia, Alactasia, Alagille Syndrome, Aland Island Eye Disease (X-Linked), Alanuria, Albers-Schonberg Disease, Albinism, Albinism, Albinismus, Albinoidism, Albright Hereditary Osteodystrophy, Alcaptonuria,
- 25 Alcaptonuria, Alcohol-Related Birth Defects, Alcoholic Embryopathy, Ald, ALD, ALD, Aldosterone, Aldosteronism With Normal Blood Pressure, Aldrich Syndrome, Alexander's Disease, Alexanders Disease, Algodystrophy, Algoneurodystrophy, Alkaptonuria, Alkaptonuric Ochronosis, Alkyl DHAP synthase deficiency, Allan-Herndon-Dudley Syndrome, Allan-Herndon Syndrome, Allan-Herndon-Dudley Mental Retardation,
- 30 Allergic Granulomatous Antitis, Allergic Granulomatous Angiitis of Cronkhite-Canada, Alobar Holoprosencephaly, Alopecia Areata, Alopecia Areata, Alopecia Celsi, Alopecia

- Cicatrisata, Alopecia Circumscripta, Alopecia-Poliosis-Uveitis-Vitiligo-Deafness-Cutaneous-Uveo-O, Alopecia Seminiversalis, Alopecia Totalis, Alopecia Universalis, Alpers Disease, Alpers Disease, Alpers Diffuse Degeneration of Cerebral Gray Matter with Hepatic Cirrhosis, Alpers Progressive Infantile Poliodystrophy, Alpha-1-Antitrypsin
- 5 Deficiency, Alpha-1 4 Glucosidase Deficiency, Alpha-1 4 Glucosidase Deficiency, Alpha-Galactosidase A Deficiency, Alpha-Galactosidase B Deficiency, Alpha-1 4 Glucosidase Deficiency, Alpha High-Density Lipoprotein Deficiency, Alpha-L-Fucosidase Deficiency Fucosidosis Type 3, Alpha-GalNAc Deficiency Schindler Type, Alpha-1 4 Glucosidase Deficiency, Alpha-L-Fucosidase Deficiency Fucosidosis Type 3, Alphalipoproteinemia,
- 10 Alpha Mannosidosis, Alpha-N-Acetylgalactosaminidase Deficiency Schindler Type, Alpha-NAGA Deficiency Schindler Type, Alpha-Neuraminidase Deficiency, Alpha-Thalassemia/mental retardation syndrome non-deletion type, Alphalipoproteinemia, Alport Syndrome, ALS, Alstroem's Syndrome, Alstroem, Alstrom Syndrome, Alternating Hemiplegia Syndrome, Alternating Hemiplegia of Childhood, Alzheimer's Disease,
- 15 Amaurotic Familial Idiocy, Amaurotic Familial Idiocy, Amaurotic Familial Idiocy Adult, Amaurotic Familial Infantile Idiocy, Amaurotic Familial Infantile Idiocy, Ambiguous Genitalia, AMC, AMD, Ameloblastoma, Amelogenesis Imperfecta, Amenorrhea-Galactorrhea Nonpuerperal, Amenorrhea-Galactorrhea-FSH Decrease Syndrome, Amenorrhea, Amino Acid Disorders, Aminoaciduria-Osteomalacia-Hyperphosphaturia
- 20 Syndrome, AMN, AMN, Amniocentesis, Amniocentesis, Amniotic Bands, Amniotic Band Syndrome, Amniotic Band Disruption Complex, Amniotic Band Sequence, Amniotic Rupture Sequence, Amputation Congenital, AMS, Amsterdam Dwarf Syndrome de Lange, Amylo-1 6-Glucosidase Deficiency, Amyloid Arthropathy of Chronic Hemodialysis, Amyloid Corneal Dystrophy, Amyloid Polyneuropathy, Amyloidosis, Amyloidosis of
- 25 Familial Mediterranean Fever, Amylopectinosis, Amyoplasia Congenita, Amyotrophic Lateral Sclerosis, Amyotrophic Lateral Sclerosis, Amyotrophic Lateral Sclerosis-Polyglucosan Bodies, AN, AN 1, AN 2, Anal Atresia, Anal Membrane, Anal Rectal Malformations, Anal Rectal Malformations, Anal Stenosis, Analine 60 Amyloidosis, Analphalipoproteinemia, Analrectal, Analrectal, Analrectal, Anaplastic Astrocytoma,
- 30 Andersen Disease, Anderson-Fabry Disease, Andersen Glycogenosis, Anderson-Warburg Syndrome, Andre Syndrome, Andre Syndrome Type II, Androgen Insensitivity, Androgen

- Insensitivity Syndrome Partial, Androgen Insensitivity Syndrome, Androgen Insensitivity Syndrome Partial, Androgenic Steroids, Anemia Autoimmune Hemolytic, Anemia Blackfan Diamond, Anemia, Congenital, Triphalangeal Thumb Syndrome, Anemia Hemolytic Cold Antibody, Anemia Hemolytic Cold Antibody, Anemia Hemolytic with  
5 PGK Deficiency, Anemia Pernicious, Anencephaly, Angelman Syndrome, Angio-Osteohypertrophy Syndrome, Angiofollicular Lymph Node Hyperplasia, Angiohemophilia, Angiokeratoma Corporis, Angiokeratoma Corporis Diffusum, Angiokeratoma Diffuse, Angiomatosis Retina, Angiomatous Lymphoid, Angioneurotic Edema Hereditary, Anhidrotic Ectodermal Dysplasia, Anhidrotic X-Linked Ectodermal  
10 Dysplasias, Aniridia, Aniridia-Ambiguous Genitalia-Mental Retardation, Aniridia Associated with Mental Retardation, Aniridia-Cerebellar Ataxia-Mental Deficiency, Aniridia Partial-Cerebellar Ataxia-Mental Retardation, Aniridia Partial-Cerebellar Ataxia-Oligophrenia, Aniridia Type I, Aniridia Type II, Aniridia-Wilms' Tumor Association, Aniridia-Wilms' Tumor-Gonadoblastoma, Ankyloblepharon-Ectodermal Defects-Cleft  
15 Lip/Palate, Ankylosing Spondylitis, Ankylosing Spondylitis, Annular groves, Anodontia, Anodontia, Anodontia Vera, Anomalous Trichromasy, Anomalous Dysplasia of Dentin, Coronal Dentin Dysplasia, Anomic Aphasia, Anophthalmia, Anorectal, Anorectal Malformations, Anosmia, Anterior Bowing of the Legs with Dwarfism, Anterior Membrane Corneal Dystrophy, Anti-Convulsant Syndrome, Anti-Epstein-Barr Virus  
20 Nuclear Antigen (EBNA) Antibody Deficiency, Antibody Deficiency, Antibody Deficiency with near normal Immunoglobulins, Antihemophilic Factor Deficiency, Antihemophilic Globulin Deficiency, Antiphospholipid Syndrome, Antiphospholipid Syndrome, Antiphospholipid Antibody Syndrome, Antithrombin III Deficiency, Antithrombin III Deficiency Classical (Type I), Antitrypsin Deficiency, Antley-Bixler  
25 Syndrome, Antoni's Palsy, Anxietas Tibialis, Aorta Arch Syndrome, Aortic and Mitral Atresia with Hypoplastic Left Heart Syndrome, Aortic Stenosis, Aortic Stenosis, Aparoschisis, APC, APECED Syndrome, Apert Syndrome, Aperts, Aphasia, Aplasia Axialis Extracorticale Congenital, Aplasia Cutis Congenita, Aplasia Cutis Congenita with Terminal Transverse Limb Defects, Aplastic Anemia, Aplastic Anemia with Congenital  
30 Anomalies, APLS, Apnea, Appalachian Type Amyloidosis, Apple Peel Syndrome, Apraxia, Apraxia, Apraxia Buccofacial, Apraxia Constructional, Apraxia Ideational,

- Apraxia Ideokinetic, Apraxia Ideomotor, Apraxia Motor, Apraxia Oculomotor, APS,  
Arachnitis, Arachnodactyly Contractural Beals Type, Arachnodactyly, Arachnoid Cysts,  
Arachnoiditis Ossificans, Arachnoiditis, Aran-Duchenne, Aran-Duchenne Muscular  
Atrophy, Aregenerative Anemia, Arginase Deficiency, Argininemia, Arginino Succinase  
5 Deficiency, Argininosuccinase Deficiency, Argininosuccinate Lyase Deficiency,  
Argininosuccinic Acid Lyase-ASL, Argininosuccinic Acid Synthetase Deficiency,  
Argininosuccinic Aciduria, Argonz-Del Castillo Syndrome, Arhinencephaly, Armenian  
Syndrome, Arnold-Chiari Malformation, Arnold-Chiari Syndrome, ARPKD, Arrhythmic  
Myoclonus, Arrhythmogenic Right Ventricular Dysplasia, Arteriohepatic Dysplasia,  
10 Arteriovenous Malformation, Arteriovenous Malformation, Arteriovenous Malformation  
of the Brain, Arteritis Giant Cell, Arthritis, Arthritis Urethritis, Arthro-Dento-  
Osteodysplasia, Arthro-Ophthalmopathy, Arthrochalasis Multiplex Congenita,  
Arthrogryposis Multiplex Congenita, Arthrogryposis Multiplex Congenita, Distal, Type  
IIA, ARVD, Arylsulfatase-B Deficiency, AS, AS, AS, AS, ASA Deficiency, Ascending  
15 Paralysis, ASD,Atrioseptal Defects, ASH, . Ashermans Syndrome, Ashkenazi Type  
Amyloidosis, ASL Deficiency, Aspartylglucosaminuria, Aspartylglycosaminuria,  
Asperger's Syndrome, Asperger's Type Autism, Asphyxiating Thoracic Dysplasia,  
Asplenia Syndrome, ASS Deficiency, Asthma, Astrocytoma Grade I (Benign),  
Astrocytoma Grade II (Benign), Asymmetric Crying Facies with Cardiac Defects,  
20 Asymmetrical septal hypertrophy, Asymptomatic Callosal Agenesis, AT, AT III  
Deficiency, AT III Variant IA, AT III Variant Ib, AT 3, Ataxia, Ataxia Telangiectasia,  
Ataxia Telangiectasia, Ataxia with Lactic Acidosis Type II, Ataxia Cerebral Palsy,  
Ataxiadynamia, Ataxiophemia, ATD, Athetoid Cerebral Palsy, Atopic Eczema, Atresia of  
Esophagus with or without Tracheoesophageal Fistula, Atrial Septal Defects, Atrial Septal  
25 Defect Primum, Atrial and Septal and Small Ventricular Septal Defect, Atrial Flutter,  
Atrial Fibrillation, Atriodigital Dysplasia, Atrioseptal Defects, Atrioventricular Block,  
Atrioventricular Canal Defect, Atrioventricular Septal Defect, Atrioventricular Septal  
Defect, Atrophia Bulborum Hereditaria, Atrophic Beriberi, Atrophy Olivopontocerebellar,  
Attention Deficit Disorder, Attention Deficit Hyperactivity Disorder, Attenuated  
30 Adenomatous Polyposis Coli, Atypical Amyloidosis, Atypical Hyperphenylalaninemia,  
Atypical Hyperphenylalaninemia, Auditory Canal Atresia, Auriculotemporal Syndrome,

- Autism, Autism Asperger's Type, Autism Dementia Ataxia and Loss of Purposeful Hand Use, Autism Infantile Autism, Autoimmune Addison's Disease, Autoimmune Hemolytic Anemia, Autoimmune Hemolytic Anemia, Autoimmune Hemolytic Anemia, Autoimmune Hemolytic Anemia, Autoimmune Hepatitis, Autoimmune-Polyendocrinopathy-Candidias,
- 5 Autoimmune Polyglandular Disease Type I, Autosomal Dominant Albinism, Autosomal Dominant Compelling Helioophthalmic Outburst Syndrome, Autosomal Dominant Desmin Distal myopathy with Late Onset, Autosomal Dominant EDS, Autosomal Dominant Emery-Dreifuss Muscular Dystrophy, Autosomal Dominant Keratoconus, Autosomal Dominant Pelizaeus-Merzbacher Brain Sclerosis, Autosomal Dominant Polycystic Kidney
- 10 Disease, Autosomal Dominant Spinocerebellar Degeneration, Autosomal Recessive Agammaglobulinemia, Autosomal Recessive Centronuclear myopathy, Autosomal Recessive Conradi-Hunermann Syndrome, Autosomal Recessive EDS, Autosomal Recessive Emery-Dreifuss Muscular Dystrophy, Autosomal Recessive Forms of Ocular Albinism, Autosomal Recessive Inheritance Agenesis of Corpus Callosum, Autosomal
- 15 Recessive Keratoconus, Autosomal Recessive Polycystic Kidney Disease, Autosomal Recessive Severe Combined Immunodeficiency, AV, AV, AVM, AVSD, AWTA, Axilla Abscess, Axonal Neuropathy Giant, Azorean Neurologic Disease, B-K Mole Syndrome, Babinski-Froelich Syndrome, BADS, Baillarger's Syndrome, Balkan Disease, Baller-Gerold Syndrome, Ballooning Mitral Valve, Balo Disease Concentric Sclerosis, Baltic
- 20 Myoclonus Epilepsy, Bannayan-Zonana syndrome (BZS), Bannayan-Riley-Ruvalcaba syndrome, Banti's Disease, Bardet-Biedl Syndrome, Bare Lymphocyte Syndrome, Barlow's syndrome, Barraquer-Simons Disease, Barrett Esophagus, Barrett Ulcer, Barth Syndrome, Barth syndrome, Bartter's Syndrome, Basal Cell Nevus Syndrome, Basedow Disease, Bassen-Kornzweig Syndrome, Batten Disease, Batten-Mayou Syndrome, Batten-
- 25 Spielmeyer-Vogt's Disease, Batten Turner Syndrome, Batten Turner Type Congenital myopathy, Batten-Vogt Syndrome, BBB Syndrome, BBB Syndrome (Opitz), BBB Syndrome, BBBG Syndrome, BCKD Deficiency, BD, BDLS, BE, Beals Syndrome, Beals Syndrome, Beals-Hecht Syndrome, Bean Syndrome, BEB, BEB, Bechterew Syndrome, Becker Disease, Becker Muscular Dystrophy, Becker Muscular Dystrophy, Becker Nevus,
- 30 Beckwith Wiedemann Syndrome, Beckwith-Syndrome, Begnez-Cesar's Syndrome, Behcet's syndrome, Behcet's Disease, Behcet's Disease, Behr 1, Behr 2, Bell's Palsy,

- Benign Acanthosis Nigricans, Benign Astrocytoma, Benign Cranial Nerve Tumors, Benign Cystinosis, Benign Essential Blepharospasm, Benign Essential Tremor, Benign Familial Hematuria, Benign Focal Amyotrophy, Benign Focal Amyotrophy of ALS, Benign Hydrocephalus, Benign Hypermobility Syndrome, Benign Keratosis Nigricans, Benign  
5 Paroxysmal Peritonitis, Benign Recurrent Hematuria, Benign Recurrent Intrahepatic Cholestasis, Benign Spinal Muscular Atrophy with Hypertrophy of the Calves, Benign Symmetrical Lipomatosis, Benign Tumors of the Central Nervous System, Berardinelli-Seip Syndrome, Berger's Disease, Beriberi, Berman Syndrome, Bernard-Horner Syndrome, Bernard-Soulier Syndrome, Besnier Prurigo, Best Disease, Beta-Alanine-  
10 Pyruvate Aminotransferase, Beta-Galactosidase Deficiency Morquio Syndrome, Beta-Glucuronidase Deficiency, Beta Oxidation Defects, Beta-oxidation Defects, Beta Thalassemia Major, Beta Thalassemia Minor, Betalipoprotein Deficiency, Bethlem myopathy, Beuren Syndrome, BH4 Deficiency, BH4 Deficiency, Biber-Haab-Dimmer Corneal Dystrophy, Bicuspid Aortic Valve, Bicuspid Aortic Valve, Biedl-Bardet, Bifid  
15 Cranium, Bifunctional Enzyme Deficiency, Bilateral Acoustic Neurofibromatosis, Bilateral Acoustic Neuroma, Bilateral Right-Sidedness Sequence, Bilateral Renal Agenesis, Bilateral Temporal Lobe Disorder, Bilious Attacks, Bilirubin Glucuronosyltransferase Deficiency Type I, Binder Syndrome, Binswanger's Disease, Binswanger's Encephalopathy, Biotinidase deficiency, Bird-Headed Dwarfism Seckel  
20 Type, Birth Defects, Birthmark, Bitemporal Forceps Marks Syndrome, Biventricular Fibrosis, Bjornstad Syndrome, B-K Mole Syndrome, Black Locks-Albinism-Deafness of Sensoneural Type (BADS), Blackfan-Diamond Anemia, Blennorrhreal Idiopathic Arthritis, Blepharophimosis, Ptosis, Epicanthus Inversus Syndrome, Blepharospasm, Blepharospasm, Blepharospasm Benign Essential, Blepharospasm Oromandibular  
25 Dystonia, Blessig Cysts, BLFS, Blindness, Bloch-Siemens Incontinentia Pigmenti Melanoblastosis Cutis Linearis, Bloch-Siemens-Sulzberger Syndrome, Bloch-Sulzberger Syndrome, Blood types, Blood type A, Blood type B, Blood type AB, Blood type O, Bloom Syndrome, Bloom-Torre-Mackacek Syndrome, Blue Rubber Bleb Nevus, Blue Baby, Blue Diaper Syndrome, BMD, BOD, BOFS, Bone Tumor-Epidermoid Cyst-  
30 Polyposis, Bonnet-Dechaume-Blanc Syndrome, Bonnevieu-Ulrich Syndrome, Book Syndrome, BOR Syndrome, BORJ, Borjeson Syndrome, Borjeson-Forssman-Lehmann

- Syndrome, Bowen Syndrome, Bowen-Conradi Syndrome, Bowen-Conradi Hutterite, Bowen-Conradi Type Hutterite Syndrome, Bowman's Layer, BPEI, BPES, Brachial Neuritis, Brachial Neuritis Syndrome, Brachial Plexus Neuritis, Brachial-Plexus-Neuropathy, Brachiocephalic Ischemia, Brachmann-de Lange Syndrome, Brachycephaly,
- 5 Brachycephaly, Brachymorphic Type Congenital, Bradycardia, Brain Tumors, Brain Tumors Benign, Brain Tumors Malignant, Branched Chain Alpha-Ketoacid Dehydrogenase Deficiency, Branched Chain Ketonuria I, Brancher Deficiency, Branchio-Oculo-Facial Syndrome, Branchio-Oto-Renal Dysplasia, Branchio-Oto-Renal Syndrome, Branchiooculofacial Syndrome, Branchiootic Syndrome, Brandt Syndrome, Brandywine
- 10 Type Dentinogenesis Imperfecta, Brandywine type Dentinogenesis Imperfecta, Breast Cancer, BRIC Syndrome, Brittle Bone Disease, Broad Beta Disease, Broad Thumb Syndrome, Broad Thumbs and Great Toes Characteristic Facies and Mental Retardation, Broad Thumb-Hallux, Broca's Aphasia, Brocq-Duhring Disease, Bronze Diabetes, Bronze Schilder's Disease, Brown Albinism, Brown Enamel Hereditary, Brown-Sequard
- 15 Syndrome, Brown Syndrome, BRRS, Brueghel Syndrome, Bruton's Agammaglobulinemia Common, BS, BSS, Buchanan's Syndrome, Budd's Syndrome, Budd-Chiari Syndrome, Buerger-Gruetz Syndrome, Bulbospinal Muscular Atrophy-X-linked, Bulldog Syndrome, Bullous Hereditaria, Bullous CIE, Bullous CIE, Bullous Congenital Ichthyosiform Erythroderma, Bullous Ichthyosis, Bullous Pemphigoid, Burkitt's Lymphoma, Burkitt's
- 20 Lymphoma African type, Burkitt's Lymphoma Non-african type, BWS, Byler's Disease, C Syndrome, C1 Esterase Inhibitor Dysfunction Type II Angioedema, C1-INH, C1 Esterase Inhibitor Deficiency Type I Angioedema, C1NH, Cacchi-Ricci Disease, CAD, CADASIL, CAH, CAH, Calcaneal Valgus, Calcaneovalgus, Calcium Pyrophosphate Dihydrate Deposits, Callosal Agenesis and Ocular Abnormalities, Calves-Hypertrophy of Spinal
- 25 Muscular Atrophy, Campomelic Dysplasia, Campomelic Dwarfism, Campomelic Syndrome, Camptodactyly-Cleft Palate-Clubfoot, Camptodactyly-Limited Jaw Excursion, Camptomelic Dwarfism, Camptomelic Syndrome, Camptomelic Syndrome Long-Limb Type, Camurati-Engelmann Disease, Camurati-Engelmann Disease, Canada-Cronkhite Disease, Canavan disease, Canavan's Disease Included, Canavan's Leukodystrophy,
- 30 Cancer, Cancer Family Syndrome Lynch Type, Cantrell Syndrome, Cantrell-Haller-Ravich Syndrome, Cantrell Pentalogy, Carbamyl Phosphate Synthetase Deficiency, Carbohydrate

- Deficient Glycoprotein Syndrome, Carbohydrate-Deficient Glycoprotein Syndrome Type Ia, Carbohydrate-Induced Hyperlipemia, Carbohydrate Intolerance of Glucose Galactose, Carbon Dioxide Acidosis, Carboxylase Deficiency Multiple, Cardiac-Limb Syndrome, Cardio-auditory Syndrome, Cardioauditory Syndrome of Jervell and Lange-Nielsen,
- 5      Cardiocutaneous Syndrome, Cardio-facial-cutaneous syndrome, Cardiofacial Syndrome Cayler Type, Cardiomegalias Glycogenica Diffusa, Cardiomegalias Glycogenica Diffusa, Cardiomyopathic Lentiginosis, Cardio myopathy, Cardio myopathy, Cardio myopathy Associated with Desmin Storage myopathy, Cardio myopathy Due to Desmin Defect, Cardio myopathy-Neutropenia Syndrome, Cardio myopathy-Neutropenia Syndrome,
- 10     Cardio myopathy-Neutropenia Syndrome Lethal Infantile Cardio myopathy, Cardiopathic Amyloidosis, Cardiospasm, Cardocardiac Syndrome, Carnitine-Acylcarnitine Translocase Deficiency, Carnitine Deficiency and Disorders, Carnitine Deficiency Primary, Carnitine Deficiency Secondary, Carnitine Deficiency Secondary to MCAD Deficiency, Carnitine Deficiency Syndrome, Carnitine Palmitoyl Transferase I & II (CPT I & II), Carnitine
- 15     Palmitoyltransferase Deficiency, Carnitine Palmitoyltransferase Deficiency Type 1, Carnitine Palmitoyltransferase Deficiency Type 2 benign classical muscular form included severe infantile form included, Carnitine Transport Defect (Primary Carnitine Deficiency), Carnosinase Deficiency, Carnosinemia, Caroli Disease, Carpenter syndrome, Carpenter's, Cartilage-Hair Hypoplasia, Cartilage-Hair Hypoplasia, Castleman's Disease, Castleman's
- 20     Disease Hyaline Vascular Type, Castleman's Disease Plasma Cell Type, Castleman Tumor, Cat Eye Syndrome, Cat's Cry Syndrome, Catalayse deficiency, Cataract-Dental Syndrome, Cataract X-Linked with Hutchinsonian Teeth, Catecholamine hormones, Catel-Manzke Syndrome, Catel-Manzke Type Palatodigital Syndrome, Caudal Dysplasia, Caudal Dysplasia Sequence, Caudal Regression Syndrome, Causalgia Syndrome Major,
- 25     Cavernomas, Cavernous Angioma, Cavernous Hemangioma, Cavernous Lymphangioma, Cavernous Malformations, Cayler Syndrome, Cazenave's Vitiligo, CBGD, CBGD, CBPS, CBPS, CCA, CCD, CCD, CCHS, CCM Syndrome, CCMS, CCO, CD, CDG1a, CDG1A, CDGS Type Ia, CDGS Type Ia, CDGS, CDI, CdLS, Celiac Disease, Celiac sprue, Celiac Sprue-Dermatitis, Cellelar Immunodeficiency with Purine Nucleoside Phosphorylase
- 30     Deficiency, Celsus' Vitiligo, Central Apnea, Central Core Disease, Central Core Disease, Central Diabetes Insipidus, Central Form Neurofibromatosis, Central Hypoventilation,

- Central Sleep Apnea, Centrifugal Lipodystrophy, Centronuclear myopathy, CEP, Cephalocele, Cephalothoracic Lipodystrophy, Ceramide Trihexosidase Deficiency, Cerebellar Agenesis, Cerebellar Aplasia, Cerebellar Hemiagenesis, Cerebellar Hypoplasia, Cerebellar Vermis Aplasia, Cerebellar Vermis Agenesis-Hypernea-Episodic Eye Moves-
- 5 Ataxia-Retardation, Cerebellar Syndrome, Cerebellarparenchymal Disorder IV, Cerebellomedullary Malformation Syndrome, Cerebellomedullary Malformation Syndrome, Cerebello-Oculocutaneous Telangiectasia, Cerebelloparenchymal Disorder IV Familial, Cerebellopontine Angle Tumor, Cerebral Arachnoiditis, Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukodystrophy, Cerebral Beriberi,
- 10 Cerebral Diplegia, Cerebral Gigantism, Cerebral Malformations Vascular, Cerebral Palsy, Cerebro-Oculorenal Dystrophy, Cerebro-Oculo-Facio-Skeletal Syndrome, Cerebrocostomandibular syndrome, Cerebrohepatorenal Syndrome, Cerebromacular Degeneration, Cerebromacular Degeneration, Cerebromuscular Dystrophy Fukuyama Type, Cerebroocular Dysgenesis, Cerebroocular Dysplasia-Muscular Dystrophy
- 15 Syndrome, Cerebrooculofacioskeletal Syndrome, Cereboretinal Arteriovenous Aneurysm, Cerebroside Lipidosis, Cerebrosidosis, Cerebrotendinous Xanthomatosis, Cerebrovascular Ferrocalcinosis, Ceroid-Lipofuscinosis Adult form, Cervical Dystonia, Cervical Dystonia, Cervico-Oculo-Acoustic Syndrome, Cervical Spinal Stenosis, Cervical Vertebral Fusion, CES, CF, CFC syndrome, CFIDS, CFND, CGD, CGF, CGF, Chalasodermia Generalized,
- 20 Chanarin Dorfman Disease, Chanarin Dorfman Syndrome, Chanarin Dorfman Ichthyosis Syndrome, Chandler's Syndrome, Charcot's Disease, Charcot-Marie-Tooth, Charcot-Marie-Tooth Disease, Charcot-Marie-Tooth Disease Variant, Charcot-Marie-Tooth-Roussy-Levy Disease, CHARGE Association, Charge Syndrome, CHARGE Syndrome, Chaund's Ectodermal Dysplasias, Chediak-Higashi Syndrome, Chediak-Higashi
- 25 Syndrome, Chediak-Steinbrinck-Higashi Syndrome, Cheilitis Granulomatosa, Cheiloschisis, Chemke Syndrome, Cheney Syndrome, Cherry Red Spot and Myoclonus Syndrome, CHF, CHH, CHH, Chiari's Disease, Chiari Malformation I, Chiari Malformation, Chiari Type I (Chiari Malformation I), Chiari Type II (Chiari Malformation II), Chiari I Syndrome, Chiari-Budd Syndrome, Chiari-Frommel Syndrome, Chiari
- 30 Malformation II, CHILD Syndrome, CHILD Ichthyosis Syndrome, CHILD Syndrome Ichthyosis, Childhood Adrenoleukodystrophy, Childhood Dermatomyositis, Childhood-

- onset Dystonia, Childhood Cyclic Vomiting, Childhood Giant Axonal Neuropathy, Childhood Hypophosphatasia, Childhood Muscular Dystrophy, CHN, Cholestasis, Cholestasis Hereditary Norwegian Type, Cholestasis Intrahepatic, Cholestasis Neonatal, Cholestasis of Oral Contraceptive Users, Cholestasis with Peripheral Pulmonary Stenosis,
- 5 Cholestasis of Pregnancy, Cholesterol Desmolase Deficiency, Cholesterol Desmolase Deficiency, Chondrodysplasia Punctata, Chondrodystrophia Calcificans Congenita, Chondrodystrophia Fetalis, Chondrodystrophic Myotonia, Chondrodystrophy, Chondrodystrophy with Clubfeet, Chondrodystrophy Epiphyseal, Chondrodystrophy Hyperplastic Form, Chondroectodermal Dysplasias, Chondrogenesis Imperfecta,
- 10 Chondrohystrophia, Chondroosteodystrophy, Choreoacanthocytosis, Chorionic Villi Sampling, Chorioretinal Anomalies, Chorioretinal Anomalies with ACC, Chorirenal Coloboma-Joubert Syndrome, Choroidal Sclerosis, Choroideremia, Chotzen Syndrome, Chotzen Syndrome, Christ-Siemens-Touraine Syndrome, Christ-Siemens-Touraine Syndrome, Christmas Disease, Christmas Tree Syndrome, Chromosome 3 Deletion of
- 15 Distal 3p, Chromosome 3 Distal 3p Monosomy, Chromosome 3-Distal 3q2 Duplication, Chromosome 3-Distal 3q2 Trisomy, Chromosome 3 Monosomy 3p2, Chromosome 3q Partial Duplication Syndrome, Chromosome 3q, Partial Trisomy Syndrome, Chromosome 3-Trisomy 3q2, Chromosome 4 Deletion 4q31-qter Syndrome, Chromosome 4 Deletion 4q32-qter Syndrome, Chromosome 4 Deletion 4q33-qter Syndrome, Chromosome 4 Long
- 20 Arm Deletion, Chromosome 4 Long Arm Deletion, Chromosome 4 Monosomy 4q, Chromosome 4-Monosomy 4q, Chromosome 4 Monosomy Distal 4q, Chromosome 4 Partial Deletion 4p, Chromosome 4, Partial Deletion of the Short Arm, Chromosome 4 Partial Monosomy of Distal 4q, Chromosome 4 Partial Monosomy 4p, Chromosome 4 Partial Trisomy 4 (q25-qter), Chromosome 4 Partial Trisomy 4 (q26 or q27-qter),
- 25 Chromosome 4 Partial Trisomy 4 (q31 or 32-qter), Chromosome 4 Partial Trisomy 4p, Chromosome 4 Partial Trisomies 4q2 and 4q3, Chromosome 4 Partial Trisomy Distal 4, Chromosome 4 Ring, Chromosome 4 4q Terminal Deletion Syndrome, Chromosome 4q-Syndrome, Chromosome 4q- Syndrome, Chromosome 4 Trisomy 4, Chromosome 4 Trisomy 4p, Chromosome 4 XY/47 XXY (Mosaic), Chromosome 5 Monosomy 5p,
- 30 Chromosome 5, Partial Deletion of the Short Arm Syndrome, Chromosome 5 Trisomy 5p, Chromosome 5 Trisomy 5p Complete (5p11-pter), Chromosome 5 Trisomy 5p Partial

- (5p13 or 14-pter), Chromosome 5p-Syndrome, Chromosome 6 Partial Trisomy 6q, Chromosome 6 Ring, Chromosome 6 Trisomy 6q2, Chromosome 7 Monosomy 7p2, Chromosome 7 Partial Deletion of Short Arm (7p2-), Chromosome 7 Terminal 7p Deletion [del (7) (p21-p22)], Chromosome 8 Monosomy 8p2, Chromosome 8 Monosomy 8p21-pter,
- 5 Chromosome 8 Partial Deletion (short arm), Chromosome 8 Partial Monosomy 8p2, Chromosome 9 Complete Trisomy 9P, Chromosome 9 Partial Deletion of Short Arm, Chromosome 9 Partial Monosomy 9p, Chromosome 9 Partial Monosomy 9p22, Chromosome 9 Partial Monosomy 9p22-pter, Chromosome 9 Partial Trisomy 9P Included, Chromosome 9 Ring, Chromosome 9 Tetrasomy 9p, Chromosome 9 Tetrasomy 9p
- 10 Mosaicism, Chromosome 9 Trisomy 9p (Multiple Variants), Chromosome 9 Trisomy 9 (pter-p21 to q32) Included, Chromosome 9 Trisomy Mosaic, Chromosome 9 Trisomy Mosaic, Chromosome 10 Distal Trisomy 10q, Chromosome 10 Monosomy, Chromosome 10 Monosomy 10p, Chromosome 10, Partial Deletion (short arm), Choromsome 10, 10p-Partial, Chromosome 10 Partial Trisomy 10q24-qter, Chromosome 10 Trisomy 10q2,
- 15 Partial Monosomy of Long Arm of Chromosome 11, Chromosome 11 Partial Monosomy 11q, Chromosome 11 Partial Trisomy, Chromosome 11 Partial Trisomy 11q13-qter, Chromosome 11 Partial Trisomy 11q21-qter, Chromosome 11 Partial Trisomy 11q23-qter, Chromosome 11q,Partial Trisomy, Chromosome 12 Isochromosome 12p Mosaic, Chromosome 13 Partial Monosomy 13q, Chromosome 13, Partial Monosomy of the Long
- 20 Arm, Chromosome 14 Ring, Chromosome 14 Trisomy, Chromosome 15 Distal Trisomy 15q, Chromosome r15, Chromosome 15 Ring, Chromosome 15 Trisomy 15q2, Chromosome 15q, Partial Duplication Syndrome, Chromosome 17 Interstitial Deletion 17p, Chromosome 18 Long Arm Deletion Syndrome, Chromosome 18 Monosomy 18p, Chromosome 18 Monosomy 18Q, Chromosome 18 Ring, Chromosome 18 Tetrasomy 18p,
- 25 Chromosome 18q- Syndrome, Chromosome 21 Mosaic 21 Syndrome, Chromosome 21 Ring, Chromosome 21 Translocation 21 Syndrome, Chromosome 22 Inverted Duplication (22pter-22q11), Chromosome 22 Partial Trisomy (22pter-22q11), Chromosome 22 Ring, Chromosome 22 Trisomy Mosaic, Chromosome 48 XXYY, Chromosome 48 XXXY, Chromosome r15, Chromosomal Triplication, Chromosome Triplication, Chromosome
- 30 Triploidy Syndrome, Chromosome X, Chromosome XXY, Chronic Acholuric Jaundice, Chronic Adhesive Arachnoiditis, Chronic Adrenocortical Insufficiency, Chronic

- Cavernositis, Chronic Congenital Aregenerative Anemia, Chronic Dysphagocytosis, Chronic Familial Granulomatosis, Chronic Familial Icterus, Chronic Fatigue Immune Dysfunction Syndrome (CFIDS), Chronic Granulomatous Disease, Chronic Guillain-Barre Syndrome, Chronic Idiopathic Jaundice, Chronic Idiopathic Polyneuritis (CIP), Chronic
- 5 Inflammatory Demyelinating Polyneuropathy, Chronic Inflammatory Demyelinating Polyradiculoneuropathy, Chronic Motor Tic, Chronic Mucocutaneous Candidiasis, Chronic Multiple Tics, Chronic Non-Specific Ulcerative Colitis, Chronic Non-Specific Ulcerative Colitis, Chronic Obliterative Cholangitis, Chronic Peptic Ulcer and Esophagitis Syndrome, Chronic Progressive Chorea, Chronic Progressive External Ophthalmoplegia
- 10 Syndrome, Chronic Progressive External Ophthalmoplegia and myopathy, Chronic Progressive External Ophthalmoplegia with Ragged Red Fibers, Chronic Relapsing Polyneuropathy, Chronic Sarcoidosis, Chronic Spasmodic Dysphonia, Chronic Vomiting in Childhood, CHS, Churg-Strauss Syndrome, Cicatricial Pemphigoid, CIP, Cirrhosis Congenital Pigmentary, Cirrhosis, Cystinuria, Citrullinemia, CJD, Classic Schindler
- 15 Disease, Classic Type Pfeiffer Syndrome, Classical Maple Syrup Urine Disease, Classical Hemophilia, Classical Form Cockayne Syndrome Type I (Type A), Classical Leigh's Disease, Classical Phenylketonuria, Classical X-Linked Pelizaeus-Merzbacher Brain Sclerosis, CLE, Cleft Lip/Palate Mucous Cysts Lower Lip PP Digital and Genital Anomalies, Cleft Lip-Palate Blepharophimosis Lagophthalmos and Hypertelorism, Cleft
- 20 Lip/Palate with Abnormal Thumbs and Microcephaly, Cleft palate-joint contractures-dandy walker malformations, Cleft Palate and Cleft Lip, Cleidocranial Dysplasia w/ Micrognathia, Absent Thumbs, & Distal Aphantangia, Cleidocranial Dysostosis, Cleidocranial Dysplasia, Click murmur syndrome, CLN1, Clonic Spasmodic, Clouston's Syndrome, Clubfoot, CMDI, CMM, CMT, CMTC, CMTX, COA Syndrome, Coarctation
- 25 of the aorta, Coarctation of the aorta, Coats' Disease, Cobblestone dysplasia, Cochin Jewish Disorder, Cockayne Syndrome, COD-MD Syndrome, COD, Coffin Lowry Syndrome, Coffin Syndrome, Coffin Siris Syndrome, COFS Syndrome, Cogan Corneal Dystrophy, Cogan Reese Syndrome, Cohen Syndrome, Cold Agglutinin Disease, Cold Antibody Disease, Cold Antibody Disease, Cold Antibody Hemolytic Anemia, Cold
- 30 Agglutinin Disease, Cold Agglutinin Disease, Colitis Ulcerative, Colitis Gravis, Colitis Gravis, Colitis Ulcerative Chronic Non-Specific Ulcerative Colitis, Collodion Baby,

- Coloboma Heart Defects Atresia of the Choanae Retardation of Growth and Development  
Genital and Urinary Anomalies and Ear Anomalies, Coloboma, Coloboma, Colonic  
Neurosis, Color blindness, Color blindness, Colour blindness, Colour blindness,  
Colpocephaly, Columnar-Like Esophagus, Combined Cone-Rod Degeneration, Combined  
5 Immunodeficiency with Immunoglobulins, Combined Mesoectodermal Dysplasia,  
Common Variable Hypogammaglobulinemia, Common Variable Immunodeficiency,  
Common Ventricle, Communicating Hydrocephalus, Complete Absense of Hypoxanthine-  
Guanine Phosphoribosyltransferase, Complete Atrioventricular Septal Defect, Complement  
Component 1 Inhibitor Deficiency, Complement Component C1 Regulatory Component  
10 Deficiency, Complete Heart Block, Complex Carbohydrate Intolerance, Complex Regional  
Pain Syndrome, Complex V ATP Synthase Deficiency, Complex I, Complex I NADH  
dehydrogenase deficiency, Complex II, Complex II Succinate dehydrogenase deficiency,  
Complex III, Complex III Ubiquinone-cytochrome c oxidoreductase deficiency, Complex  
IV, Complex IV Cytochrome c oxidase deficiency, Complex IV Deficiency, Complex V,  
15 Cone-Rod Degeneration, Cone-Rod Degeneration Progressive, Cone Dystrophy, Cone-  
Rod Dystrophy, Confluent Reticular Papillomatosis, Congenital with low PK Kinetics,  
Congenital Absence of Abdominal Muscles, Congenital Absence of the Thymus and  
Parathyroids, Congenital Achromia, Congenital Addison's Disease, Congenital Adrenal  
Hyperplasia, Congenital Adreanal Hyperplasia, Congenital Afibrinogenemia, Congenital  
20 Alveolar Hypoventilation, Congenital Anemia of Newborn, Congenital Bilateral  
Persylvian Syndrome, Congenital Brown Syndrome, Congenital Cardiovascular Defects,  
Congenital Central Hypoventilation Syndrome, Congenital Cerebral Palsy, Congenital  
Cervical Synostosis, Congenital Clasped Thumb with Mental Retardation, Congenital  
Contractural Arachnodactyly, Congenital Contractures Multiple with Arachnodactyly,  
25 Congenital Cyanosis, Congenital Defect of the Skull and Scalp, Congenital Dilatation of  
Intrahepatic Bile Duct, Congenital Dysmyelinating Neuropathy, Congenital  
Dysphagocytosis, Congenital Dysplastic Angiectasia, Congenital Erythropoietic Porphyria,  
Congenital Erythropoietic Porphyria, Congenital Factor XIII Deficiency, Congenital  
Failure of Autonomic Control of Respiration, Congenital Familial Nonhemolytic Jaundice  
30 Type I, Congenital Familial Protracted Diarrhea, Congenital Form Cockayne Syndrome  
Type II (Type B), Congenital Generalized Fibromatosis, Congenital German Measles,

- Congenital Giant Axonal Neuropathy, Congenital Heart Block, Congenital Heart Defects, Congenital Hemidysplasia with Ichthyosis Erythroderma and Limb Defects, Congenital Hemolytic Jaundice, Congenital Hemolytic Anemia, Congenital Hepatic Fibrosis, Congenital Hereditary Corneal Dystrophy, Congenital Hereditary Lymphedema,
- 5 Congenital Hyperchondroplasia, Congenital Hypomyelinating Polyneuropathy, Congenital Hypomyelination Neuropathy, Congenital Hypomyelination, Congenital Hypomyelination Neuropathy, Congenital Hypomyelination (Onion Bulb) Polyneuropathy, Congenital Ichthyosiform Erythroderma, Congenital Keratoconus, Congenital Lactic Acidosis, Congenital Lactose Intolerance, Congenital Lipodystrophy, Congenital Liver Cirrhosis,
- 10 Congenital Lobar Emphysema, Congenital Localized Emphysema, Congenital Macroglossia, Congenital Medullary Stenosis, Congenital Megacolon, Congenital Melanocytic Nevus, Congenital Mesodermal Dysmorphodystrophy, Congenital Mesodermal Dystrophy, Congenital Microvillus Atrophy, Congenital Multiple Arthrogryposis, Congenital Myotonic Dystrophy, Congenital Neuropathy caused by
- 15 Hypomyelination, Congenital Pancytopenia, Congenital Pernicious Anemia, Congenital Pernicious Anemia due to Defect of Intrinsic Factor, Congenital Pernicious Anemia due to Defect of Intrinsic Factor, Congenital Pigmentary Cirrhosis, Congenital Porphyria, Congenital Proximal myopathy Associated with Desmin Storage myopathy, Congenital Pulmonary Emphysema, Congenital Pure Red Cell Anemia, Congenital Pure Red Cell
- 20 Aplasia, Congenital Retinal Blindness, Congenital Retinal Cyst, Congenital Retinitis Pigmentosa, Congenital Retinoschisis, Congenital Rod Disease, Congenital Rubella Syndrome, Congenital Scalp Defects with Distal Limb Reduction Anomalies, Congenital Sensory Neuropathy, Congenital SMA with arthrogryposis, Congenital Spherocytic Anemia, Congenital Spondyloepiphyseal Dysplasia, Congenital Tethered Cervical Spinal
- 25 Cord Syndrome, Congenital Tyrosinosis, Congenital Varicella Syndrome, Congenital Vascular Cavernous Malformations, Congenital Vascular Veils in the Retina, Congenital Word Blindness, Congenital Wandering Spleen (Pediatric), Congestive Cardio myopathy, Conical Cornea, Conjugated Hyperbilirubinemia, Conjunctivitis, Conjunctivitis Ligneous, Conjunctivo-Urethro-Synovial Syndrome, Conn's Syndrome, Connective Tissue Disease,
- 30 Conradi Disease, Conradi Hunermann Syndrome, Constitutional Aplastic Anemia, Constitutional Erythroid Hypoplasia, Constitutional Eczema, Constitutional Liver

- Dysfunction, Constitutional Thrombopathy, Constricting Bands Congenital, Constrictive Pericarditis with Dwarfism, Continuous Muscle Fiber Activity Syndrome, Contractural Arachnodactyly, Contractural Arachnodactyly, Contractures of Feet Muscle Atrophy and Oculomotor Apraxia, Convulsions, Cooley's anemia, Copper Transport Disease,
- 5 Coproporphyrinia Porphyria Hepatica, Cor Triatriatum, Cor Triatriatum Sinistrum, Cor Triloculare Bivatriatum, Cor Biloculare, Cori Disease, Cornea Dystrophy, Corneal Amyloidosis, Corneal Clouding-Cutis Laxa-Mental Retardation, Corneal Dystrophy, Cornelia de Lange Syndrome, Coronal Dentine Dysplasia, Coronary Artery Disease, Coronary Heart Disease, Corpus Callosum Agenesis, Cortical-Basal Ganglionic
- 10 Degeneration, Corticalis Deformaris, Cortico-Basal Ganglionic Degeneration (CBGD), Corticobasal Degeneration, Corticosterone Methloxiidase Deficiency Type I, Corticosterone Methyloxidase Deficiency Type II, Cortisol, Costello Syndrome, Cot Death, COVESDEM Syndrome, COX, COX Deficiency, COX Deficiency French-Canadian Type, COX Deficiency Infantile Mitochondrial myopathy de Toni-Fanconi-
- 15 Debre included, COX Deficiency Type Benign Infantile Mitochondrial Myopathy, CP, CPEO, CPEO with myopathy, CPEO with Ragged-Red Fibers, CPPD Familial Form, CPT Deficiency, CPTD, Cranial Arteritis, Cranial Meningoencephalocele, Cranio-Oro-Digital Syndrome, Craniocarpotarsal dystrophy, Craniocle, Craniodigital Syndrome-Mental Retardation Scott Type, Craniofacial Dysostosis, Craniofacial Dysostosis-PD Arteriosus-
- 20 Hypertrichosis-Hypoplasia of Labia, Craniofrontonasal Dysplasia, Craniometaphyseal Dysplasia, Cranioradial Digital Syndrome, Cranioradial Digital Syndrome Type II, Craniostenosis Crouzon Type, Craniostenosis, Craniostenosis, Craniosynostosis-Choanal Atresia-Radial Humeral Synostosis, Craniosynostosis-Hypertrichosis-Facial and Other Anomalies, Craniosynostosis Midfacial Hypoplasia and Foot Abnormalities, Craniosynostosis Primary,
- 25 Craniosynostosis-Radial Aplasia Syndrome, Craniosynostosis with Radial Defects, Cranium Bifidum, CREST Syndrome, CREST Syndrome, Creutzfeldt Jakob Disease, Cri du Chat Syndrome, Crib Death, Crigler Najjar Syndrome Type I, Crohn's Disease, Crohn's Disease, Cronkhite-Canada Syndrome, Cross Syndrome, Cross' Syndrome, Cross-McKusick-Breen Syndrome, Crouzon, Crouzon Syndrome, Crouzon Craniofacial
- 30 Dysostosis, Cryoglobulinemia Essential Mixed, Cryptophthalmos-Syndactyly Syndrome, Cryptorchidism-Dwarfism-Subnormal Mentality, Crystalline Corneal Dystrophy of

- Schnyder, CS, CSD, CSID, CSO, CST Syndrome, Curly Hair-Ankyloblepharon-Nail Dysplasia, Curschmann-Batten-Steinert Syndrome, Curth Macklin Type Ichthyosis Hystric, Curth-Macklin Type, Cushing's, Cushing Syndrome, Cushing's III, Cutaneous Malignant Melanoma Hereditary, Cutaneous Porphyrias, Cutis Laxa, Cutis Laxa, Cutis
- 5 Laxa-Growth Deficiency Syndrome, Cutis Marmorata Telangiectatica Congenita, CVI, CVID, CVS, CVS, Cyclic vomiting syndrome, Cystic Disease of the Renal Medulla, Cystic Disease of the Renal Medulla, Cystic Hygroma, Cystic Fibrosis, Cystic Lymphangioma, Cystine-Lysine-Arginine-Ornithinuria, Cystine Storage Disease, Cystinosis, Cystinuria, Cystinuria with Dibasic Aminoaciduria, Cystinuria Type I,
- 10 Cystinuria Type II, Cystinuria Type III, Cysts of the Renal Medulla Congenital, Cysts of the Renal Medulla Congenital, Cytochrome C Oxidase Deficiency, D.C., Dacryosialoadenopathy, Dacryosialoadenopathia, Dalpro, Dalton, Daltonism, Danbolt-Cross Syndrome, Dancing Eyes-Dancing Feet Syndrome, Dandy-Walker Syndrome, Dandy-Walker Cyst, Dandy-Walker Deformity, Dandy Walker Malformation, Danish
- 15 Cardiac Type Amyloidosis (Type III), Darier Disease, Davidson's Disease, Davies' Disease, DBA, DBS, DC, DD, De Barsy Syndrome, De Barsy-Moens-Diercks Syndrome, de Lange Syndrome, De Morsier Syndrome, De Santis Cacchione Syndrome, de Toni-Fanconi Syndrome, Deafness Congenital and Functional Heart Disease, Deafness-Dwarfism-Retinal Atrophy, Deafness-Functional Heart Disease, Deafness
- 20 Onychodystrophy Osteodystrophyand Mental Retardation, Deafness and Pili Torti Bjornstad Type, Deafness Sensorineural with Imperforate Anus and Hypoplastic Thumbs, Debrancher Deficiency, Deciduous Skin, Defect of Enterocyte Intrinsic Factor Receptor, Defect of Enterocyte Intrinsic Factor Receptor, Defect in Natural Killer Lymphocytes, Defect of Renal Reabsorption of Carnitine, Deficiency of Glycoprotein Neuraminidase,
- 25 Deficiency of Mitochondrial Respiratory Chain Complex IV, Deficiency of Platelet Glycoprotein Ib, Deficiency of Von Willebrand Factor Receptor, Deficiency of Short-Chain Acyl-CoA Dehydrogenase (ACADS, Deformity with Mesomelic Dwarfism, Degenerative Chorea, Degenerative Lumbar Spinal Stenosis, Degos Disease, Degos-Kohlmeier Disease, Degos Syndrome, DEH, Dejerine-Roussy Syndrome, Dejerine Sottas
- 30 Disease, Deletion 9p Syndrome Partial, Deletion 11q Syndrome Partial, Deletion 13q Syndrome Partial, Delleman-Oorthuys Syndrome, Delleman Syndrome, Dementia with

- Lobar Atrophy and Neuronal Cytoplasmic Inclusions, Demyelinating Disease, DeMyer Syndrome, Dentin Dysplasia Coronal, Dentin Dysplasia Radicular, Dentin Dysplasia Type I, Dentin Dysplasia Type II, Dentinogenesis Imperfecta Brandywine type, Dentinogenesis Imperfecta Shields Type, Dentinogenesis Imperfecta Shields Type, Dentinogenesis Imperfecta Type III, Dentinogenesis Imperfecta Type III, Dento-Oculo-Osseous Dysplasia, Dento-Oculo-Osseous Dysplasia, Dentooculocutaneous Syndrome, Denys-Drash Syndrome, Depakene, DepakeneTM exposure, Depakote, Depakote Sprinkle, Depigmentation-Gingival Fibromatosis-Microphthalmia, Dercum Disease, Dercum Disease, Dermatitis Atopic, Dermatitis Exfoliativa, Dermatitis Herpetiformis, Dermatitis Multiformis, Dermatochalaşia Generalized, Dermatolysis Generalized, Dermatomegaly, Dermatomyositis sine myositis, Dermatomyositis, Dermatosparaxis, Dermatostomatitis Stevens Johnson Type, Desbuquois Syndrome, Desmin Storage myopathy, Desquamation of Newborn, Deuteranomaly, Deuteranomaly, Developmental Reading Disorder, Developmental Gerstmann Syndrome, Devergie Disease, Devic Disease, Devic Syndrome, Dextrocardia- Bronchiectasis and Sinusitis, Dextrocardia with Situs Inversus, DGS, DGSX Golabi-Rosen Syndrome Included, DH, DHAP alkyl transferase deficiency, DHBS Deficiency, DHBS Deficiency, DHOF, DHPR Deficiency, DHPR Deficiency, Diabetes Insipidus, Diabetes Insipidus Diabetes Mellitus Optic Atrophy and Deafness, Diabetes Insipidus Neurohypophyseal, Diabetes Insulin Dependent, Diabetes Mellitus, Diabetes Mellitus Addison's Disease Myxedema, Diabetic Acidosis, Diabetic Bearded Woman Syndrome, Diamond-Blackfan Anemia, Diaphragmatic Apnea, Diaphyseal Aclasis, Diastrophic Dwarfism, Diastrophic Dysplasia, Diastrophic Nanism Syndrome, Dicarboxylic Aminoaciduria, Dicarboxylicaciduria Caused by Defect in Beta-Oxidation of Fatty Acids, Dicarboxylicaciduria due to Defect in Beta-Oxidation of Fatty Acids, Dicarboxylicaciduria due to MCADH Deficiency, Dichromasy, Dicker-Opitz, DIDMOAD, Diencephalic Syndrome, Diencephalic Syndrome of Childhood, Diencephalic Syndrome of Emaciation, Dienoyl-CoA Reductase Deficiency, Diffuse Cerebral Degeneration in Infancy, Diffuse Degenerative Cerebral Disease, Diffuse Idiopathic Skeletal Hyperostosis, Diffusum-Glycopeptiduria, DiGeorge Syndrome, DiGeorge Syndrome, Digital-Oro-Cranio Syndrome, Digit-Oto-Palatal Syndrome, Digit-Oto-Palatal Syndrome Type I, Digit-Oto-Palatal Syndrome Type II, Dihydrobiopterin Synthetase Deficiency, Dihydrobiopterin

- Synthetase Deficiency, Dihydropteridine Reductase Deficiency, Dihydropteridine Reductase Deficiency, Dihydroxyacetonephosphate synthase, Dilated (Congestive) Cardio myopathy, Dimitri Disease, Diplegia of Cerebral Palsy, Diplo-Y Syndrome, Disaccharidase Deficiency, Disaccharide Intolerance I, Discoid Lupus, Discoid Lupus Erythematosus, DISH, Disorder of Cornification, Disorder of Cornification Type I, Disorder of Cornification 4, Disorder of Cornification 6, Disorder of Cornification 8, Disorder of Cornification 9 Netherton's Type, Disorder of Cornification 11 Phytanic Acid Type, Disorder of Cornification 12 (Neutral Lipid Storage Type), Disorder of Conification 13, Disorder of Cornification 14, Disorder of Cornification 14 Trichothiodystrophy Type, Disorder of Cornification 15 (Keratitis Deafness Type), Disorder of Cornification 16, Disorder of Cornification 18 Erythrokeratodermia Variabilis Type, Disorder of Cornification 19, Disorder of Cornification 20, Disorder of Cornification 24, Displaced Spleen, Disseminated Lupus Erythematosus, Disseminated Neurodermatitis, Disseminated Sclerosis, Distal 11q Monosomy, Distal 11q- Syndrome, Distal Arthrogryposis Multiplex Congenita Type IIA, Distal Arthrogryposis Multiplex Congenita Type IIA, Distal Arthrogryposis Type IIA, Distal Arthrogryposis Type 2A, Distal Duplication 6q, Distal Duplication 10q, Dup(10q) Syndrome, Distal Duplication 15q, Distal Monosomy 9p, Distal Trisomy 6q, Distal Trisomy 10q Syndrome, Distal Trisomy 11q, Divalproex, DJS, DKC, DLE, DLPIII, DM, DMC Syndrome, DMC Disease, DMD, DNS Hereditary, DOC I, DOC 2, DOC 4, DOC 6 (Harlequin Type), DOC 8 Curth-Macklin Type, DOC 11 Phytanic Acid Type, DOC 12 (Neutral Lipid Storage Type), DOC 13, DOC 14, DOC 14 Trichothiodystrophy Type, DOC 15 (Keratitis Deafness Type); DOC 16, DOC 16 Unilateral Hemidysplasia Type, DOC 18, DOC 19, DOC 20, DOC 24, Dohle's Bodies-Myopathy, Dolichospondylic Dysplasia, Dolichostenomelia, Dolichostenomelia Syndrome, Dominant Type Kenny-Caffe Syndrome, Dominant Type Myotonia Congenita, Donahue Syndrome, Donath-Landsteiner Hemolytic Anemia, Donath-Landsteiner Syndrome, DOOR Syndrome, DOORS Syndrome, Dopa-responsive Dystonia (DRD), Dorfman Chanarin Syndrome, Dowling-Meara Syndrome, Down Syndrome, DR Syndrome, Drash Syndrome, DRD, Dreifuss-Emery Type Muscular Dystrophy with Contractures, Dressler Syndrome, Drifting Spleen, Drug-induced Acanthosis Nigricans, Drug-induced Lupus Erythematosus, Drug-related Adrenal Insufficiency, Drummond's

- Syndrome, Dry Beriberi, Dry Eye, DTD, Duane's Retraction Syndrome, Duane Syndrome, Duane Syndrome Type IA 1B and 1C, Duane Syndrome Type 2A 2B and 2C, Duane Syndrome Type 3A 3B and 3C, Dubin Johnson Syndrome, Dubowitz Syndrome, Duchenne, Duchenne Muscular Dystrophy, Duchenne's Paralysis, Duhring's Disease,
- 5 Duncan Disease, Duncan's Disease, Duodenal Atresia, Duodenal Stenosis, Duodenitis, Duplication 4p Syndrome, Duplication 6q Partial, Dupuytren's Syndrome, Dupuytren's Contracture, Dutch-Kennedy Syndrome, Dwarfism, Dwarfism Campomelic, Dwarfism Cortical Thickening of the Tubular Bones & Transient Hypocalcemia, Dwarfism Levi's Type, Dwarfism Metatropic, Dwarfism-Onychodysplasia, Dwarfism-Pericarditis,
- 10 Dwarfism with Renal Atrophy and Deafness, Dwarfism with Rickets, DWM, Dyggve Melchior Clausen Syndrome, Dysautonomia Familial, Dysbetalipoproteinemia Familial, Dyschondrodysplasia with Hemangiomas, Dyschondrosteosis, Dyschromatosis Universalis Hereditaria, Dysencephalia Splanchnocystica, Dyskeratosis Congenita, Dyskeratosis Congenita Autosomal Recessive, Dyskeratosis Congenita Scoggins Type, Dyskeratosis
- 15 Congenita Syndrome, Dyskeratosis Follicularis Vegetans, Dyslexia, Dysmyelogenic Leukodystrophy, Dysmyelogenic Leukodystrophy-Megalobare, Dysphonia Spastica, Dysplasia Epiphysialis Punctata, Dysplasia Epiphyseal Hemimelica, Dysplasia of Nails With Hypodontia, Dysplasia Cleidocranial, Dysplasia Fibrous, Dysplasia Gigantism SyndromeX-Linked, Dysplasia Osteodental, Dysplastic Nevus Syndrome, Dysplastic
- 20 Nevus Syndrome, Dysplastic Nevus Type, Dyssynergia Cerebellaris Myoclonica, Dyssynergia Esophagus, Dystonia, Dystonia, Dystopia Canthorum, Dystopia Canthorum, Dystrophia Adiposogenitalis, Dystrophia Endothelialis Cornea, Dystrophia Mesodermalis, Dystrophic Epidermolysis Bullosa, Dystrophic Epidermolysis Bullosa, Dystrophy, Asphyxiating Thoracic, Dystrophy Myotonic, E-D Syndrome, Eagle-Barrett Syndrome,
- 25 Eales Retinopathy, Eales Disease, Ear Anomalies-Contractures-Dysplasia of Bone with Kyphoscoliosis, Ear Patella Short Stature Syndrome, Early Constraint Defects, Early Hypercalcemia Syndrome with Elfin Facie, Early-onset Dystonia, Eaton Lambert Syndrome, EB, Ebstein's anomaly, EBV Susceptibility (EBVS), EBVS, ECD, ECPSG, Ectodermal Dysplasias, Ectodermal Dysplasia Anhidrotic with Cleft Lip and Cleft Palate,
- 30 Ectodermal Dysplasia-Exocrine Pancreatic Insufficiency, Ectodermal Dysplasia Rapp-Hodgkin type, Ectodermal and Mesodermal Dysplasia Congenital, Ectodermal and

- Mesodermal Dysplasia with Osseous Involvement, Ectodermosis Erosiva Pluriorficialis, Ectopia Lentis, Ectopia Vesicae, Ectopic ACTH Syndrome, Ectopic Adrenocorticotropic Hormone Syndrome, Ectopic Anus, Ectrodactilia of the Hand, Ectrodactyly, Ectrodactyly-Ectodermal Dysplasia-Clefting Syndrome, Ectrodactyly Ectodermal Dysplasias Clefting
- 5 Syndrome, Ectrodactyly Ectodermal Dysplasia Cleft Lip/Cleft Palate, Eczema, Eczema-Thrombocytopenia-Immunodeficiency Syndrome, EDA, EDMD, EDS, EDS Arterial-Eccymotic Type, EDS Arthrochalasia, EDS Classic Severe Form, EDS Dysfibronectinemic, EDS Gravis Type, EDS Hypermobility, EDS Kyphoscoliotic, EDS Kyphoscoliosis, EDS Mitis Type, EDS Ocular-Scoliotic, EDS Progeroid, EDS
- 10 Periodontosis, EDS Vascular, EEC Syndrome, EFE, EHBA, EHK, Ehlers Danlos Syndrome, Ehlers-Danlos syndrome, Ehlers Danlos IX, Eisenmenger Complex, Eisenmenger's complex, Eisenmenger Disease, Eisenmenger Reaction, Eisenmenger Syndrome, Eisenmenger Syndrome, Ekbom Syndrome, Ekman-Lobstein Disease, Ektrodactyly of the Hand, Ektrodactyly of the Hand, EKV, Elastin fiber disorders,
- 15 Elastorrhexis Generalized, Elastosis Dystrophica Syndrome, Elective Mutism (obsolete), Elective Mutism, Electrocardiogram (ECG or EKG), Electron Transfer Flavoprotein (ETF) Dehydrogenase Deficiency: (GAII & MADD), Electrophysiologic study (EPS), Elephant Nails From Birth, Elephantiasis Congenita Angiomatosa, Hemangiectatic Hypertrophy, Elfin Facies with Hypercalcemia, Ellis-van Creveld Syndrome, Ellis Van Creveld
- 20 Syndrome, Embryoma Kidney, Embryonal Adenomyosarcoma Kidney, Embryonal Carcinosarcoma Kidney, Embryonal Mixed Tumor Kidney, EMC, Emery Dreyfus Muscular Dystrophy, Emery-Dreifuss Muscular Dystrophy, Emery-Dreifuss Syndrome, EMF, EMG Syndrome, Empty Sella Syndrome, Encephalitis Periaxialis Diffusa, Encephalitis Periaxialis Concentrica, Encephalocele, Encephalofacial Angiomatosis,
- 25 Encephalopathy, Encephalotrigeminal Angiomatosis, Enchondromatosis with Multiple Cavernous Hemangiomas, Endemic Polyneuritis, Endocardial Cushion Defect, Endocardial Cushion Defect, Endocardial Cushion Defects, Endocardial Dysplasia, Endocardial Fibroelastosis (EFE), Endogenous Hypertriglyceridemia, Endolymphatic Hydrops, Endometrial Growths, Endometriosis, Endomyocardial Fibrosis, Endothelial
- 30 Corneal Dystrophy Congenital, Endothelial Epithelial Corneal Dystrophy, Endothelium, Engelmann Disease, Enlarged Tongue, Enterocolitis, Enterocyte Cobalamin

- Malabsorption, Eosinophia Syndrome, Eosinophilic Cellulitis, Eosinophilic Fasciitis,  
Eosinophilic Granuloma, Eosinophilic Syndrome, Epidermal Nevus Syndrome,  
Epidermolysis bullosa, Epidermolysis Bullosa, Epidermolysis Bullosa Acquisita,  
Epidermolysis Bullosa Hereditaria, Epidermolysis Bullosa Letalias, Epidermolysis  
5 Hereditaria Tarda, Epidermolytic Hyperkeratosis, Epidermolytic Hyperkeratosis (Bullous  
CIE), Epilepsia Procursiva, Epilepsy, Epinephrine, Epiphyseal Changes and High Myopia,  
Epiphyseal Osteochondroma Benign, Epiphysealis Hemimelica Dysplasia, Episodic-  
Abnormal Eye Movement, Epithelial Basement Membrane Corneal Dystrophy, Epithelial  
Corneal Dystrophy of Meesmann Juvenile, Epitheliomatosis Multiplex with Nevus,  
10 Epithelium, Epival, EPS, Epstein-Barr Virus-Induced Lymphoproliferative Disease in  
Males, Erb-Goldflam syndrome, Erdheim Chester Disease, Erythema Multiforme  
Exudativum, Erythema Polymorphe Stevens Johnson Type, Erythroblastophthisis,  
Erythroblastosis Fetalis, Erythroblastosis Neonatorum, Erythroblastotic Anemia of  
Childhood, Erythrocyte Phosphoglycerate Kinase Deficiency, Erythrogenesis Imperfecta,  
15 Erythrokeratoderma Progressiva Symmetrica, Erythrokeratoderma Progressiva  
Symmetrica Ichthyosis, Erythrokeratoderma Variabilis, Erythrokeratoderma Variabilis,  
Erythrokeratoderma Variabilis Type, Erythrokeratolysis Hiemalis, Erythrokeratolysis  
Hiemalis, Erythrokeratolysis Hiemalis, Erythropoietic Porphyrias, Erythropoietic  
Porphyria, Escobar Syndrome, Esophageal Atresia, Esophageal Aperistalsis, Esophagitis-  
20 Peptic Ulcer, Esophagus Atresia and/or Tracheoesophageal Fistula, Essential Familial  
Hyperlipemia, Essential Fructosuria, Essential Hematuria, Essential Hemorrhagic  
Thrombocythemia, Essential Hemorrhagic Thrombocythemia, Essential Mixed  
Cryoglobulinemia, Essential Moschowitz Disease, Essential Thrombocythemia, Essential  
Thrombocythemia, Essential Thrombocytopenia, Essential Thrombocytosis, Essential  
25 Thrombocytosis, Essential Tremor, Esterase Inhibitor Deficiency, Estren-Dameshek  
variant of Fanconi Anemia, Estrogen-related Cholestasis, ET, ET, ETF, Ethylmalonic  
Adipicaciduria, Eulenburg Disease, pc, EVCS, Exaggerated Startle Reaction, Exencephaly,  
Exogenous Hypertriglyceridemia, Exomphalos-Macroglossia-Gigantism Syndrom,  
Exophthalmic Goiter, Expanded Rubella Syndrome, Exstrophy of the Bladder, EXT,  
30 External Chondromatosis Syndrome, Extrahepatic Biliary Atresia, Extramedullary  
Plasmacytoma, Exudative Retinitis, Eye Retraction Syndrome, FA1, FAA, Fabry Disease,

- FAC, FACB, FACD, FACE, FACF, FACG, FACH, Facial Nerve Palsy, Facial Paralysis, Facial Ectodermal Dysplasias, Facial Ectodermal Dysplasia, Facio-Scapulo-Humeral Dystrophy, Facio-Auriculo-Vertebral Spectrum, Facio-cardio-cutaneous syndrome, Facio-Fronto-Nasal Dysplasia, Faciocutaneoskeletal Syndrome, Faciodigitogenital syndrome,
- 5 Faciogenital dysplasia, Faciogenitopopliteal Syndrome, Faciopalatoosseous Syndrome, Faciopalatoosseous Syndrome Type II, Facioscapulohumeral muscular dystrophy, Factitious Hypoglycemia, Factor VIII Deficiency, Factor IX Deficiency, Factor IX Deficiency, Factor XI Deficiency, Factor XII deficiency, Factor XIII Deficiency, Fahr Disease, Fahr's Disease, Failure of Secretion Gastric Intrinsic Factor, Fairbank Disease,
- 10 Fallot's Tetralogy, Familial Acrogeria, Familial Acrogeria, Familial Acromicria, Familial Acromicria, Familial Adenomatous Colon Polyposis, Familial Adenomatous Polyposis with Extraintestinal Manifestations, Familial Alobar Holoprosencephaly, Familial Alpha-Lipoprotein Deficiency, Familial Amyotrophic Chorea with Acanthocytosis, Familial Arrhythmic Myoclonus, Familial Articular Chondrocalcinosis, Familial Atypical Mole-
- 15 Malignant Melanoma Syndrome, Familial Broad Beta Disease, Familial Calcium Gout, Familial Calcium Pyrophosphate Arthropathy, Familial Chronic Obstructive Lung Disease, Familial Continuous Skin Peeling, Familial Cutaneous Amyloidosis, Familial Dysproteinemia, Familial Emphysema, Familial Enteropathy Microvillus, Familial Foveal Retinoschisis, Familial Hibernation Syndrome, Familial High Cholesterol, Familial
- 20 Hemochromatosis, Familial High Blood Cholesterol, Familial High-Density Lipoprotein Deficiency, Familial High Serum Cholesterol, Familial Hyperlipidemia, Familial Hypoproteinemia with Lymphangioreticular Enteropathy, Familial Jaundice, Familial Juvenile Nephronophthisis-Associated Ocular Anomaly, Familial Lichen Amyloidosis (Type IX), Familial Lumbar Stenosis, Familial Lymphedema Praecox, Familial Mediterranean Fever,
- 25 Familial Multiple Polyposis, Familial Nuchal Bleb, Familial Paroxysmal Polyserositis, Familial Polyposis Coli, Familial Primary Pulmonary Hypertension, Familial Renal-Glycosuria, Familial Splenic Anemia, Familial Startle Disease, Familial Visceral Amyloidosis (Type VIII), FAMMM, FANCA, FANCB, FANCC, FANCD, FANCE, Fanconi Panmyelopathy, Fanconi Pancytopenia, Fanconi II, Fanconi's Anemia, Fanconi's
- 30 Anemia Type I, Fanconi's Anemia Complementation Group, Fanconi's Anemia Complementation Group A, Fanconi's Anemia Complementation Group B, Fanconi's

Anemia Complementation Group C, Fanconi's Anemia Complementation Group D,  
Fanconi's Anemia Complementation Group E, Fanconi's Anemia Complementation Group  
G, Fanconi's Anemia Complementation Group H, Fanconi's Anemia Estren-Dameshek  
Variant, FANF, FANG, FANH, FAP, FAPG, Farber's Disease, Farber's  
5 Lipogranulomatosis, FAS, Fasting Hypoglycemia, Fat-Induced Hyperlipemia, Fatal  
Granulomatous Disease of Childhood, Fatty Oxidation Disorders, Fatty Liver with  
Encephalopathy, FAV, FCH, FCMD, FCS Syndrome, FD, FDH, Febrile Mucocutaneous  
Syndrome Stevens Johnson Type, Febrile Neutrophilic Dermatosis Acute, Febrile  
Seizures, Feinberg's syndrome, Feissinger-Leroy-Reiter Syndrome, Female Pseudo-Turner  
10 Syndrome, Femoral Dysgenesis Bilateral-Robin Anomaly, Femoral Dysgenesis Bilateral,  
Femoral Facial Syndrome, Femoral Hypoplasia-Unusual Facies Syndrome, Fetal Alcohol  
Syndrome, Fetal Anti-Convulsant Syndrome, Fetal Cystic Hygroma, Fetal Effects of  
Alcohol, Fetal Effects of Chickenpox, Fetal Effects of Thalidomide, Fetal Effects of  
Varicella Zoster Virus, Fetal Endomyocardial Fibrosis, Fetal Face Syndrome, Fetal Iritis  
15 Syndrome, Fetal Transfusion Syndrome, Fetal Valproate Syndrome, Fetal Valproic Acid  
Exposure Syndrome, Fetal Varicella Infection, Fetal Varicella Zoster Syndrome, FFDD  
Type II, FG Syndrome, FG DY, FHS, Fibrin Stabilizing Factor Deficiency, Fibrinase  
Deficiency, Fibrinoid Degeneration of Astrocytes, Fibrinoid Leukodystrophy,  
Fibrinoligase Deficiency, Fibroblastoma Perineural, Fibrocystic Disease of Pancreas,  
20 Fibrodysplasia Ossificans Progressiva, Fibroelastic Endocarditis, Fibromyalgia,  
Fibromyalgia-Fibromyositis, Fibromyositis, Fibrosing Cholangitis, Fibrositis, Fibrous  
Ankylosis of Multiple Joints, Fibrous Cavernositis, Fibrous Dysplasia, Fibrous Plaques of  
the Penis, Fibrous Sclerosis of the Penis, Fickler-Winkler Type, Fiedler Disease, Fifth  
Digit Syndrome, Filippi Syndrome, Finnish Type Amyloidosis (Type V), First Degree  
25 Congenital Heart Block, First and Second Branchial Arch Syndrome, Fischer's Syndrome,  
Fish Odor Syndrome, Fissured Tongue, Flat Adenoma Syndrome, Flatau-Schilder Disease,  
Flavin Containing Monooxygenase 2, Floating Beta Disease, Floating-Harbor Syndrome,  
Floating Spleen, Floppy Infant Syndrome, Floppy Valve Syndrome, Fluent aphasia, FMD,  
FMF, FMO Adult Liver Form, FMO2, FND, Focal Dermal Dysplasia Syndrome, Focal  
30 Dermal Hypoplasia, Focal Dermato-Phalangeal Dysplasia, Focal Dystonia, Focal Epilepsy,  
Focal Facial Dermal Dysplasia Type II, Focal Neuromyotonia, FODH, Folling Syndrome,

- Fong Disease, FOP, Forbes Disease, Forbes-Albright Syndrome, Forestier's Disease, Forsius-Eriksson Syndrome (X-Linked), Fothergill Disease, Fountain Syndrome, Foveal Dystrophy Progressive, FPO Syndrome Type II, FPO, Fraccaro Type Achondrogenesis (Type IB), Fragile X syndrome, Franceschetti-Zwahlen-Klein Syndrome, Francois 5 Dyscephaly Syndrome, Francois-Neetens Speckled Dystrophy, Flecked Corneal Dystrophy, Fraser Syndrome, FRAXA, FRDA, Fredrickson Type I Hyperlipoproteinemia, Freeman-Sheldon Syndrome, Freire-Maia Syndrome, Frey's Syndrome, Friedreich's Ataxia, Friedreich's Ataxia, Friedreich's Disease, Friedreich's Tabes, FRNS, Froelich's Syndrome, Frommel-Chiari Syndrome, Frommel-Chiari Syndrome Lactation-Uterus 10 Atrophy, Frontodigital Syndrome, Frontofacionasal Dysostosis, Frontofacionasal Dysplasia, Frontonasal Dysplasia, Frontonasal Dysplasia with Coronal Craniosynostosis, Fructose-1-Phosphate Aldolase Deficiency, Fructosemia, Fructosuria, Fryns Syndrome, FSH, FSHD, FSS, Fuchs Dystrophy, Fucosidosis Type 1, Fucosidosis Type 2, Fucosidosis Type 3, Fukuhara Syndrome, Fukuyama Disease, Fukuyama Type Muscular Dystrophy, 15 Fukuyama Type Muscular Dystrophy, Fumarylacetoacetate deficiency, Furrowed Tongue, G Syndrome, G6PD Deficiency, G6PD, GA I, GA IIB, GA IIA, GA II, GAI & MADD, Galactorrhea-Amenorrhea Syndrome Nonpuerperal, Galactorrhea-Amenorrhea without Pregnancy, Galactosamine-6-Sulfatase Deficiency, Galactose-1-Phosphate Uridyl Transferase Deficiency, Galactosemia, GALB Deficiency, Galloway-Mowat Syndrome, 20 Galloway Syndrome, GALT Deficiency, Gammaglobulin Deficiency, GAN, Ganglioside Neuraminidase Deficiency, Ganglioside Sialidase Deficiency, Gangliosidosis GM1 Type 1, Gangliosidosis GM2 Type 2, Gangliosidosis Beta Hexosaminidase B Defecency, Gardner Syndrome, Gardner Syndrome, Gargoylism, Garies-Mason Syndrome, Gasser Syndrome, Gastric Intrinsic Factor Failure of Secretion, Enterocyte Cobalamin, 25 Gastrinoma, Gastritis, Gastroesophageal Laceration-Hemorrhage, Gastrointestinal Polyposis and Ectodermal Changes, Gastroschisis, Gaucher Disease, Gaucher-Schlagenhauf, Gayet-Wernicke Syndrome, GBS, GCA, GCM Syndrome, GCPS, Gee-Herter Disease, Gee-Thaysen Disease, Gehrig's Disease, Gelineau's Syndrome, Genee-Wiedemann Syndrome, Generalized Dystonia, Generalized Familial Neuromyotonia, 30 Generalized Fibromatosis, Generalized Flexion Epilepsy, Generalized Glycogenosis, Generalized Glycogenosis, Generalized Hyperhidrosis, Generalized Lipofuscinosis,

- Generalized Myasthenia Gravis, Generalized Myotonia, Generalized Sporadic Neuromytonia, Genetic Disorders, Genital Defects, Genital and Urinary Tract Defects, Genital and Urinary Tract Defects, Gerstmann Syndrome, Gerstmann Tetrad, GHBP, GHD, GHR, Giant Axonal Disease, Giant Axonal Neuropathy, Giant Benign Lymphoma,
- 5 Giant Cell Glioblastoma Astrocytoma, Giant Cell Arteritis, Giant Cell Disease of the Liver, Giant Cell Hepatitis, Giant Cell of Newborns Cirrhosis, Giant Cyst of the Retina, Giant Lymph Node Hyperplasia, Giant Platelet Syndrome Hereditary, Giant Tongue, gic Macular Dystrophy, Gilbert's Disease, Gilbert Syndrome, Gilbert-Dreyfus Syndrome, Gilbert-Dreyfus Syndrome, Gilbert-Lereboullet Syndrome, Gilford Syndrome, Gilles de la
- 10 Tourette's syndrome, Gillespie Syndrome, Gingival Fibromatosis-Abnormal Fingers Nails Nose Ear Splenomegaly, GLA Deficiency, GLA, GLB1, Glioma Retina, Global aphasia, Globoid Leukodystrophy, Glossoptosis Micrognathia and Cleft Palate, Glucocerebrosidase deficiency, Glucocerebrosidosis, Glucose-6-Phosphate Dehydrogenase Deficiency, Glucose-6-Phosphate Tranport Defect, Glucose-6-Phosphate Translocase Deficiency,
- 15 Glucose-G-Phosphatase Deficiency, Glucose-Galactose Malabsorption, Glucose-Galactose Malabsorption, Glucosyl Ceramide Lipidosis, Glutaric Aciduria I, Glutaric Acidemia I, Glutaric Acidemia II, Glutaric Aciduria II, Glutaric Aciduria Type II, Glutaric Aciduria Type III, Glutaricacidemia I, Glutaricacidemia II, Glutaricaciduria I, Glutaricaciduria II, Glutaricaciduria Type IIA, Glutaricaciduria Type IIB, Glutaryl-CoA Dehydrogenase
- 20 Deficiency, Glutaurate-Aspartate Transport Defect, Gluten-Sensitive Enteropathy, Glycogen Disease of Muscle Type VII, Glycogen Storage Disease I, Glycogen Storage Disease III, Glycogen Storage Disease IV, Glycogen Storage Disease Type V, Glycogen Storage Disease VI, Glycogen Storage Disease VII, Glycogen Storage Disease VIII, Glycogen Storage Disease Type II, Glycogen Storage Disease-Type II, Glycogenosis,
- 25 Glycogenosis Type I, Glycogenosis Type IA, Glycogenosis Type IB, Glycogenosis Type II, Glycogenosis Type II, Glycogenosis Type III, Glycogenosis Type IV, Glycogenosis Type V, Glycogenosis Type VI, Glycogenosis Type VII, Glycogenosis Type VIII, Glycolic Aciduria, Glycolic Aciduria, Glycolipid Lipidosis, GM2 Gangliosidosis Type 1, GM2 Gangliosidosis Type 1, GNPTA, Goitrous Autoimmune Thyroiditis, Goldenhar
- 30 Syndrome, Goldenhar-Gorlin Syndrome, Goldscheider's Disease, Goltz Syndrome, Goltz-Gorlin Syndrome, Gonadal Dysgenesis 45 X, Gonadal Dysgenesis XO, Goniodysgenesis-

- Hypodontia, Goodman Syndrome, Goodman, Goodpasture Syndrome, Gordon Syndrome, Gorlin's Syndrome, Gorlin-Chaudhry-Moss Syndrome, Gottron Erythrokeratoderma Congenitalis Progressiva Symmetrica, Gottron's Syndrome, Gougerot-Carteaud Syndrome, Grand Mal Epilepsy, Granular Type Corneal Dystrophy, Granulomatous Arteritis,  
5 Granulomatous Colitis, Granulomatous Dermatitis with Eosinophilia, Granulomatous Ileitis, Graves Disease, Graves' Hyperthyroidism, Graves' Disease, Greig Cephalopolysyndactyly Syndrome, Groenouw Type I Corneal Dystrophy, Groenouw Type II Corneal Dystrophy, Gronblad-Strandberg Syndrome, Grotton Syndrome, Growth Hormone Receptor Deficiency, Growth Hormone Binding Protein Deficiency, Growth  
10 Hormone Deficiency, Growth-Mental Deficiency Syndrome of Myhre, Growth Retardation-Rieger Anomaly, GRS, Gruber Syndrome, GS, GSD6, GSD8, GTS, Guanosine Triphosphate-Cyclohydrolase Deficiency, Guanosine Triphosphate-Cyclohydrolase Deficiency, Guenther Porphyria, Guerin-Stern Syndrome, Guillain-Barré, Guillain-Barre Syndrome, Gunther Disease, H Disease, H. Gottron's Syndrome, H.  
15 Gottron's Syndrome, Habit Spasms, HAE, Hageman Factor Deficiency, Hageman factor, Haim-Munk Syndrome, Hajdu-Cheney Syndrome, Hajdu Cheney, HAL Deficiency, Hall-Pallister Syndrome, Hallermann-Streiff-Francois syndrome, Hallermann-Streiff Syndrome, Hallervorden-Spatz Disease, Hallervorden-Spatz Syndrome, Hallopeau-Siemens Disease, Hallux Duplication Postaxial Polydactyly and Absence of Corpus Callosum, Halushi-  
20 Behcet's Syndrome, Hamartoma of the Lymphatics, Hand-Schueller-Christian Syndrome, HANE, Hanhart Syndrome, Happy Puppet Syndrome, Harada Syndrome, HARD +/-E Syndrome, HARD Syndrome, Hare Lip, Harlequin Fetus, Harlequin Type DOC 6, Harlequin Type Ichthyosis, Harlequin Type Ichthyosis, Harley Syndrome, Harrington Syndrome, Hart Syndrome, Hartnup Disease, Hartnup Disorder, Hartnup Syndrome,  
25 Hashimoto's Disease, Hashimoto-Pritzker Syndrome, Hashimoto's Syndrome, Hashimoto's Thyroiditis, Hashimoto's Thyroiditis, Hashimoto-Pritzker Syndrome, Hay Well's Syndrome, Hay-Wells Syndrome of Ectodermal Dysplasia, HCMM, HCP, HCTD, HD, Heart-Hand Syndrome (Holt-Oram Type), Heart Disease, Hecht Syndrome, HED, Heerferdt-Waldenstrom and Lofgren's Syndromes, Hegglin's Disease, Heinrichsbauer Syndrome, Hemangiomas, Hemangioma Familial, Hemangioma-Thrombocytopenia Syndrome, Hemangiomatosis Chondrodstrophica, Hemangiomatous Branchial Clefts-Lip  
30

- Pseudocleft Syndrome, Hemifacial Microsomia, Hemimegalencephaly, Hemiparesis of Cerebral Palsy, Hemiplegia of Cerebral Palsy, Hemisection of the Spinal Cord, Hemochromatosis, Hemochromatosis Syndrome, Hemodialysis-Related Amyloidosis, Hemoglobin Lepore Syndromes, Hemolytic Anemia of Newborn, Hemolytic Cold  
5 Antibody Anemia, Hemolytic Disease of Newborn, Hemolytic-Uremic Syndrome, Hemolytic-Uremic Syndrome, Hemophilia, Hemophilia A, Hemophilia B, Hemophilia B Factor IX, Hemophilia C, Hemorrhagic Dystrophic Thrombocytopenia, Hemorrhagica Aleukia, Hemosiderosis, Hepatic Fructokinase Deficiency, Hepatic Phosphorylase Kinase Deficiency, Hepatic Porphyria, Hepatic Porphyrias, Hepatic Porphyrias, Hepatic Veno-  
10 Occlusive Diseases, Hepato-Renal Syndrome, Hepatolenticular Degeneration, Hepatophosphorylase Deficiency, Hepatorenal Glycogenosis, Hepatorenal Syndrome, Hepatorenal Tyrosinemia, Hereditary Acromelalgia, Hereditary Alkaptonuria, Hereditary Amyloidosis, Hereditary Angioedema, Hereditary Areflexic Dystasia, Heredopathia Atactica Polyneuritiformis, Hereditary Ataxia, Hereditary Ataxia, Hereditary Ataxia  
15 Friedrich's Type, Hereditary Benign Acanthosis Nigricans, Hereditary Cerebellar Ataxia, Hereditary Chorea, Hereditary Chronic Progressive Chorea, Hereditary Connective Tissue Disorders, Hereditary Coproporphyrina, Hereditary Coproporphyrina Porphyria, Hereditary Cutaneous Malignant Melanoma, Hereditary Deafness-Retinitis Pigmentosa, Heritable Disorder of Zinc Deficiency, Hereditary DNS, Hereditary Dystopic Lipidosis, Hereditary  
20 Emphysema, Hereditary Fructose Intolerance, Hereditary Hemorrhagic Telangiectasia, Hereditary Hemorrhagic Telangiectasia Type I, Hereditary Hemorrhagic Telangiectasia Type II, Hereditary Hemorrhagic Telangiectasia Type III, Hereditary Hyperuricemia and Choroathetosis Syndrome, Hereditary Leptocytosis Major, Hereditary Leptocytosis Minor, Hereditary Lymphedema, Hereditary Lymphedema Tarda, Hereditary  
25 Lymphedema Type I, Hereditary Lymphedema Type II, Hereditary Motor Sensory Neuropathy, Hereditary Motor Sensory Neuropathy I, Hereditary Motor Sensory Neuropathy Type III, Hereditary Nephritis, Hereditary Nephritis and Nerve Deafness, Hereditary Nephropathic Amyloidosis, Hereditary Nephropathy and Deafness, Hereditary Nonpolyposis Colorectal Cancer, Hereditary Nonpolyposis Colorectal Carcinoma,  
30 Hereditary Nonspherocytic Hemolytic Anemia, Hereditary Onychoosteodysplasia, Hereditary Optic Neuroretinopathy, Hereditary Polyposis Coli, Hereditary Sensory and

- Autonomic Neuropathy Type I, Hereditary Sensory and Autonomic Neuropathy Type II,  
Hereditary Sensory and Autonomic Neuropathy Type III, Hereditary Sensory Motor  
Neuropathy, Hereditary Sensory Neuropathy type I, Hereditary Sensory Neuropathy Type  
I, Hereditary Sensory Neuropathy Type II, Hereditary Sensory Neuropathy Type III,  
5 Hereditary Sensory Radicular Neuropathy Type I, Hereditary Sensory Radicular  
Neuropathy Type I, Hereditary Sensory Radicular Neuropathy Type II, Hereditary Site  
Specific Cancer, Hereditary Spherocytic Hemolytic Anemia, Hereditary Spherocytosis,  
Hereditary Tyrosinemia Type I, Heritable Connective Tissue Disorders, Herlitz Syndrome,  
Hermans-Herzberg Phakomatosis, Hermansky-Pudlak Syndrome, Hermansky-Pudlak  
10 Syndrome, Hermaphroditism, Herpes Zoster, Herpes Iris Stevens-Johnson Type, Hers  
Disease, Heterozygous Beta Thalassemia, Hexoaminidase Alpha-Subunit Deficiency  
(Variant B), Hexoaminidase Alpha-Subunit Deficiency (Variant B), HFA, HFM, HGPS,  
HH, HHHO, HHRH, HHT, Hiatal Hernia-Microcephaly-Nephrosis Galloway Type,  
Hidradenitis Suppurativa, Hidrosadenitis Axillaris, Hidrosadenitis Suppurativa, Hidrotic  
15 Ectodermal Dysplasias, HIE Syndrome, High Imperforate Anus, High Potassium, High  
Scapula, HIM, Hirschsprung's Disease, Hirschsprung's Disease Acquired, Hirschsprung  
Disease Polydactyly of Ulnar & Big Toe and VSD, Hirschsprung Disease with Type D  
Brachydactyly, Hirsutism, HIS Deficiency, Histidine Ammonia-Lyase (HAL) Deficiency,  
Histidase Deficiency, Histidinemia, Histidinemia, Histiocytosis, Histiocytosis X, HLHS,  
20 HLP Type II, HMG, HMI, HMSN I, HNHA, HOCM, Hodgkin Disease, Hodgkin's  
Disease, Hodgkin's Lymphoma, Hollaender-Simons Disease, Holmes-Adie Syndrome,  
Holocarboxylase Synthetase Deficiency, Holoprosencephaly, Holoprosencephaly  
Malformation Complex, Holoprosencephaly Sequence, Holt-Oram Syndrome, Holt-Oram  
Type Heart-Hand Syndrome, Homocystinemia, Homocystinuria, Homocystinuria,  
25 Homogentisic Acid Oxidase Deficiency, Homogentisic Aciduria, Homozygous Alpha-1-  
Antitrypsin Deficiency, HOOD, Horner Syndrome, Horton's disease, HO\$ , HOS1,  
Houston-Harris Type Achromodogenesis (Type IA), HPS, HRS, HS, HS, HS, HS, HS,  
HSAN Type I, HSAN Type II, HSAN-III, HSMN, HSMN Type III, HSN I, HSN-III,  
Huebner-Herter Disease, Hunner's Patch, Hunner's Ulcer, Hunter Syndrome, Hunter  
30 Syndrome, Hunter-Thompson Type Acromesomelic Dysplasia, Huntington's Chorea,  
Huntington's Disease, Hurler Disease, Hurler Disease, Hurler Syndrome, Hurler-Scheie

- Syndrome, HUS, HUS, Hutchinson-Gilford Progeria Syndrome, Hutchinson-Gilford Syndrome, Hutchinson-Weber-Peutz Syndrome, Hutchinson-Weber-Peutz Syndrome, Hutterite Syndrome Bowen-Conradi Type, Hyaline Panneuropathy, Hydranencephaly, Hydrocephalus, Hydrocephalus Agyria and Retinal Dysplasia, Hydrocephalus Internal  
5 Dandy-Walker Type, Hydrocephalus Noncommunicating Dandy-Walker Type, Hydrocephaly, Hydronephrosis With Peculiar Facial Expression, Hydroxylase Deficiency, Hygroma Colli, Hyper-IgE Syndrome, Hyper-IgM Syndrome, Hyper IgM Syndrome, Hyperaldosteronism, Hyperaldosteronism With Hypokalemic Alkalosis, Hyperaldosteronism Without Hypertension, Hyperammonemia, Hyperammonemia Due to  
10 Carbamylphosphate Synthetase Deficiency, Hyperammonemia Due to Ornithine Transcarbamylase Deficiency, Hyperammonemia Type II, Hyper-Beta Carnosinemia, Hyperbilirubinemia I, Hyperbilirubinemia II, Hypercalcemia Familial with Nephrocalcinosis and Indicanuria, Hypercalcemia-Supravalvar Aortic Stenosis, Hypercalciuric Rickets, Hypercapnic acidosis, Hypercatabolic Protein-Losing Enteropathy,  
15 Hyperchloremic acidosis, Hypercholesterolemia, Hypercholesterolemia Type IV, Hyperchylomicronemia, Hypercystinuria, Hyperekplexia, Hyperextensible joints, Hyperglobulinemic Purpura, Hyperglycinemia with Ketoacidosis and Lactic Acidosis Propionic Type, Hyperglycinemia Nonketotic, Hypergonadotropic Hypogonadism, Hyperimmunoglobulin E Syndrome, Hyperimmunoglobulin E-Recurrent Infection  
20 Syndrome, Hyperimmunoglobulinemia E-Staphylococcal, Hyperkalemia, Hyperkinetic Syndrome, Hyperlipemic Retinitis, Hyperlipidemia I, Hyperlipidemia IV, Hyperlipoproteinemia Type I, Hyperlipoproteinemia Type III, Hyperlipoproteinemia Type IV, Hyperoxaluria, Hyperphalangy-Clinodactyly of Index Finger with Pierre Robin Syndrome, Hyperphenylalanemia, Hyperplastic Epidermolysis Bullosa, Hyperpnea,  
25 Hyperpotassemia, Hyperprebeta-Lipoproteinemia, Hyperprolinemia Type I, Hyperprolinemia Type II, Hypersplenism, Hypertelorism with Esophageal Abnormalities and Hypospadias, Hypertelorism-Hypospadias Syndrome, Hypertrophic Cardiomyopathy, Hypertrophic Interstitial Neuropathy, Hypertrophic Interstitial Neuritis, Hypertrophic Interstitial Radiculoneuropathy, Hypertrophic Neuropathy of Refsum, Hypertrophic  
30 Obstructive Cardiomyopathy, Hyperuricemia Choroathetosis Self-mutilation Syndrome, Hyperuricemia-Oligophrenia, Hypervalinemia, Hypocalcified (Hypomineralized) Type,

- Hypochondrogenesis, Hypochondroplasia, Hypogammaglobulinemia,  
 Hypogammaglobulinemia Transient of Infancy, Hypogenital Dystrophy with Diabetic  
 Tendency, Hypoglossia-Hypodactylia Syndrome, Hypoglycemia, Hypoglycemia,  
 Exogenous Hypoglycemia, Hypoglycemia with Macroglossia, Hypoglycosylation  
 5 Syndrome Type 1a, Hypoglycosylation Syndrome Type 1a, Hypogonadism with Anosmia,  
 Hypogonadotropic Hypogonadism and Anosmia, Hypohidrotic Ectodermal Dysplasia,  
 Hypohidrotic Ectodermal Dysplasia Autosomal Dominant type, Hypohidrotic Ectodermal  
 Dysplasias Autorecessive, Hypokalemia, Hypokalemic Alkalosis with Hypercalciuria,  
 Hypokalemic Syndrome, Hypolactasia, Hypomaturation Type (Snow-Capped Teeth),  
 10 Hypomelanosis of Ito, Hypomelia-Hypotrichosis-Facial Hemangioma Syndrome,  
 Hypomyelination Neuropathy, Hypoparathyroidism, Hypophosphatasia,  
 Hypophosphatemic Rickets with Hypercalcemia, Hypopigmentation, Hypopigmentation,  
 Hypopigmented macular lesion, Hypoplasia of the Depressor Anguli Oris Muscle with  
 Cardiac Defects, Hypoplastic Anemia, Hypoplastic Congenital Anemia, Hypoplastic  
 15 Chondrodystrophy, Hypoplastic Enamel-Onycholysis-Hypohidrosis, Hypoplastic  
 (Hypoplastic-Explastic) Type, Hypoplastic Left Heart Syndrome, Hypoplastic Left Heart  
 Syndrome, Hypoplastic-Triphalangeal Thumbs, Hypopotassemia Syndrome, Hypospadias-  
 Dysphagia Syndrome, Hyposmia, Hypothalamic Hamartoblastoma Hypopituitarism  
 Imperforate Anus Polydactyly, Hypothalamic Infantilism-Obesity, Hypothyroidism,  
 20 Hypotonia-Hypomentia-Hypogonadism-Obesity Syndrome, Hypoxanthine-Guanine  
 Phosphoribosyltransferase Defect (Complete Absense of), I-Cell Disease, Iatrogenic  
 Hypoglycemia, IBGC, IBIDS Syndrome, IBM, IBS, IC, I-Cell Disease, ICD, ICE  
 Syndrome Cogan-Reese Type, Icelandic Type Amyloidosis (Type VI), I-Cell Disease,  
 Ichthyosiform Erythroderma Corneal Involvement and Deafness, Ichthyosiform  
 25 Erythroderma Hair Abnormality Growth and Men, Ichthyosiform Erythroderma with  
 Leukocyte Vacuolation, Ichthyosis, Ichthyosis Congenita, Ichthyosis Congenital with  
 Trichothiodystrophy, Ichthyosis Hystrix, Ichthyosis Hystrix Gravior, Ichthyosis Linearis  
 Circumflexa, Ichthyosis Simplex, Ichthyosis Tay Syndrome, Ichthyosis Vulgaris,  
 Ichthyosis Vulgaris, Ichthyotic Neutral Lipid Storage Disease, Icteric Leptospirosis,  
 30 Icterohemorrhagic Leptospirosis, Icterus (Chronic Familial), Icterus Gravis Neonatorum,  
 Icterus Intermittens Juvenalis, Idiopathic Alveolar Hypoventilation, Idiopathic

- Amyloidosis, Idiopathic Arteritis of Takayasu, Idiopathic Basal Ganglia Calcification (IBGC), Idiopathic Brachial Plexus Neuropathy, Idiopathic Cervical Dystonia, Idiopathic Dilatation of the Pulmonary Artery, Idiopathic Dilatation of the Pulmonary Artery, Idiopathic Facial Palsy, Idiopathic Familial Hyperlipemia, Idiopathic Hypertrophic
- 5 Subaortic Stenosis, Idiopathic Hypoproteinemia, Idiopathic Immunoglobulin Deficiency, Idiopathic Neonatal Hepatitis, Idiopathic Non-Specific Ulcerative Colitis, Idiopathic Non-Specific Ulcerative Colitis, Idiopathic Peripheral Periphlebitis, Idiopathic Pulmonary Fibrosis, Idiopathic Refractory Sideroblastic Anemia, Idiopathic Refractory Sideroblastic Anemia, Idiopathic Renal Hematuria, Idiopathic Steatorrhea, Idiopathic Thrombocythemia,
- 10 Idiopathic Thrombocythemia, Idiopathic Thrombocytopenic Purpura, Idiopathic Thrombocytopenia Purpura (ITP), IDPA, IDPA, IgA Nephropathy, IgA Nephropathy, IHSS, Ileitis, Ileocolitis, Illinois Type Amyloidosis, ILS, IM, IMD2, IMD5, IMD5, Immune Defect due to Absence of Thymus, Immune Hemolytic Anemia Paroxysmal Cold, Immunodeficiency with Ataxia Telangiectasia, Immunodeficiency Cellular with Abnormal
- 15 Immunoglobulin Synthesis, Immunodeficiency Common Variable Unclassifiable, Immunodeficiency with Hyper-IgM, Immunodeficiency with Leukopenia, Immunodeficiency-2, Immunodeficiency-5 (IMD5), Immunoglobulin Deficiency, Imperforate Anus, Imperforate Anus with Hand Foot and Ear Anomalies, Imperforate Nasolacrimal Duct and Premature Aging Syndrome, Impotent Neutrophil Syndrome,
- 20 Inability To Open Mouth Completely And Short Finger-Flexor, INAD, INAD, Inborn Error of Urea Synthesis Arginase Type, Inborn Error of Urea Synthesis Arginino Succinic Type, Inborn Errors of Urea Synthesis Carbamyl Phosphate Type, Inborn Error of Urea Synthesis Citrullinemia Type, Inborn Errors of Urea Synthesis Glutamate Synthetase Type, INCL, Inclusion body myositis, Incomplete Atrioventricular Septal Defect, Incomplete
- 25 Testicular Feminization, Incomplete Testicular Feminization, Incontinentia Pigmenti, Incontinentia Pigmenti, Incontinenti Pigmenti Achromians, Index Finger Anomaly with Pierre Robin Syndrome, Indiana Type Amyloidosis (Type II), Indolent systemic mastocytosis, Infantile Acquired Aphasia, Infantile Autosomal Recessive Polycystic Kidney Disease, Infantile Beriberi, Infantile Cerebral Ganglioside, Infantile Cerebral
- 30 Ganglioside, Infantile Cerebral Paralysis, Infantile Cystinosis, Infantile Epileptic, Infantile Fanconi Syndrome with Cystinosis, Infantile Finnish Type Neuronal Ceroid

- Lipofuscinosis, Infantile Gaucher Disease, Infantile Hypoglycemia, Infantile Hypophosphatasia, Infantile Lobar Emphysema, Infantile Myoclonic Encephalopathy, Infantile Myoclonic Encephalopathy and Polymyoclonia, Infantile Myofibromatosis, Infantile Necrotizing Encephalopathy, Infantile Neuronal Ceroid Lipofuscinosis, Infantile
- 5 Neuroaxonal Dystrophy, Infantile Onset Schindler Disease, Infantile Phytanic Acid Storage Disease, Infantile Refsum Disease (IRD), Infantile Sipoidosis GM-2 Gangliosideosis (Type S), Infantile Sipoidosis GM-2 Gangliosideosis (Type S, Infantile Sleep Apnea, Infantile Spasms, Infantile Spinal Muscular Atrophy (all types), Infantile Spinal Muscular Atrophy ALS, Infantile Spinal Muscular Atrophy Type I, Infantile Type
- 10 Neuronal Ceroid Lipofuscinosis, Infectious Jaundice, Inflammatory Breast Cancer, Inflammatory Linear Nevus Sebaceous Syndrome, Iniencephaly, Insulin Resistant Acanthosis Nigricans, Insulin Lipodystrophy, Insulin dependent Diabetes, Intention Myoclonus, Intermediate Cystinosis, Intermediate Maple Syrup Urine Disease, Intermittent Ataxia with Pyruvate Dehydrogenase Deficiency, Intermittent Ataxia with Pyruvate
- 15 Dehydrogenase Deficiency, Intermittent Maple Syrup Urine Disease, Internal Hydrocephalus, Interstitial Cystitis, Interstitial Deletion of 4q Included, Interstitial Deletion of 4q- Included, Intestinal Lipodystrophy, Intestinal Lipophagic Granulomatosis, Intestinal Lymphangiectasia, Intestinal Polyposis I, Intestinal Polyposis II, Intestinal Polyposis II, Intestinal Polyposis III, Intestinal Polyposis-Cutaneous Pigmentation
- 20 Syndrome, Intestinal Polyposis-Cutaneous Pigmentation Syndrome, Intestinal Pseudoobstruction with External Ophthalmoplegia, Intracranial Neoplasm, Intracranial Tumors, Intracranial Vascular Malformations, Intrauterine Dwarfism, Intrauterine Synechiae, Inverted Smile And Occult Neuropathic Bladder, Iowa Type Amyloidosis (Type IV), IP, IPA, Iridocorneal Endothelial Syndrome, Iridocorneal Endothelial (ICE)
- 25 Syndrome Cogan-Resse Type, Iridogoniogenesis With Somatic Anomalies, Iris Atrophy with Corneal Edema and Glaucoma, Iris Nevus Syndrome, Iron Overload Anemia, Iron Overload Anemia, Iron Overload Disease, Irritable Bowel Syndrome, Irritable Colon Syndrome, Isaacs Syndrome, Isaacs-Merten Syndrome, Ischemic Cardiomyopathy, Isolated Lissencephaly Sequence, Isoleucine 33 Amyloidosis, Isovaleric Acid
- 30 CoA Dehydrogenase Deficiency, Isovaleric Acidaemia, Isovalericacidemia, Isovaleryl CoA Carboxylase Deficiency, ITO Hypomelanosis, ITO, ITP, ITP, IVA, Ivemark

- Syndrome, Iwanoff Cysts, Jackknife Convulsion, Jackson-Weiss Craniosynostosis, Jackson-Weiss Syndrome, Jacksonian Epilepsy, Jacobsen Syndrome, Jadassohn-Lewandowsky Syndrome, Jaffe-Lichenstein Disease, Jakob's Disease, Jakob-Creutzfeldt Disease, Janeway I, Janeway Dysgammaglobulinemia, Jansen Metaphyseal Dysostosis,
- 5 Jansen Type Metaphyseal Chondrodysplasia, Jarcho-Levin Syndrome, Jaw-Winking, JBS, JBS, JDMS, Jegher's Syndrome, Jegher's Syndrome, Jejunal Atresia, Jejunitis, Jejunoileitis, Jervell and Lange-Nielsen Syndrome, Jeune Syndrome, JMS, Job Syndrome, Job-Buckley Syndrome, Johanson-Blizzard Syndrome, John Dalton, Johnson-Stevens Disease, Jonston's Alopecia, Joseph's Disease, Joseph's Disease Type I, Joseph's Disease
- 10 Type II, Joseph's Disease Type III, Joubert Syndrome, Joubert-Bolthauser Syndrome, JRA, JRA, Juberg Hayward Syndrome, Juberg-Marsidi Syndrome, Juberg-Marsidi Mental Retardation Syndrome, Jumping Frenchmen, Jumping Frenchmen of Maine, Juvenile Arthritis, Juvenile Arthritis, Juvenile Autosomal Recessive Polycystic Kidney Disease, Juvenile Cystinosis, Juvenile (Childhood) Dermatomyositis (JDMS), Juvenile Diabetes,
- 15 Juvenile Gaucher Disease, Juvenile Gout Choroathetosis and Mental Retardation Syndrome, Juvenile Intestinal Malabsorption of Vit B12, Juvenile Intestinal Malabsorption of Vitamin B12, Juvenile Macular Degeneration, Juvenile Pernicious Anemia, Juvenile Retinoschisis, Juvenile Rheumatoid Arthritis, Juvenile Rheumatoid Arthritis, Juvenile Spinal Muscular Atrophy Included, Juvenile Spinal Muscular Atrophy ALS Included,
- 20 Juvenile Spinal Muscular Atrophy Type III, Juxta-Articular Adiposis Dolorosa, Juxta-Articular Adiposis Dolorosa, Juxtaglomerular Hyperplasia, Kabuki Make-Up Syndrome, Kahler Disease, Kallmann Syndrome, Kanner Syndrome, Kanzaki Disease, Kaposi Disease (not Kaposi Sarcoma), Kappa Light Chain Deficiency, Karsch-Neugebauer Syndrome, Karsch-Neugebauer Syndrome, Kartagener Syndrome-Chronic Sinobronchial Disease and
- 25 Dextrocardia, Kartagener Triad, Kasabach-Merritt Syndrome, Kast Syndrome, Kawasaki Disease, Kawasaki Syndrome, KBG Syndrome, KD, Kearns-Sayre Disease, Kearns-Sayre Syndrome, Kearns-Sayre Syndrome, Kennedy Disease, Kennedy Syndrome, Kennedy Type Spinal and Bulbar Muscular Atrophy, Kennedy-Stefanis Disease, Kenny Disease, Kenny Syndrome, Kenny Type Tubular Stenosis, Kenny-Caffe Syndrome, Kera.
- 30 Palmoplant. Con. Pes Planus Ony. Periodon. Arach., Keratitis Ichthyosis Deafness Syndrome, Keratoconus, Keratoconus, Keratoconus Posticus Circumscriptus, Keratolysis,

- Keratolysis Exfoliativa Congenita, Keratolytic Winter Erythema, Keratomalacia, Keratosis Follicularis, Keratosis Follicularis Spinulosa Decalvans, Keratosis Follicularis Spinulosa Decalvans Ichthyosis, Keratosis Nigricans, Keratosis Palmoplantaris with Periodontopathia and Onychogryposis, Keratosis Palmoplantaris Congenital Pes Planus Onychogryposis
- 5 Periodontosis Arachnodactyly, Keratosis Palmoplantaris Congenital, Pes Planus, Onychogryphosis, Periodontosis, Arachnodactyly, Acroosteolysis, Keratosis Rubra Figurata, Keratosis Seborrheica, Ketoacid Decarboxylase Deficiency, Ketoaciduria, Ketotic Glycinemia, Ketotic Glycinemia, KFS, KID Syndrome, Kidney Agenesis, Kidneys Cystic-Retinal Aplasia Joubert Syndrome, Killian Syndrome, Killian/Teschler-Nicola
- 10 Syndrome, Kiloh-Nevin syndrome III, Kinky Hair Disease, Kinsbourne Syndrome, Kleeblattschadel Deformity, Kleine-Levin Syndrome, Kleine-Levin Hibernation Syndrome, Klinefelter, Klippel-Feil Syndrome, Klippel-Feil Syndrome Type I, Klippel-Feil Syndrome Type II, Klippel-Feil Syndrome Type III, Klippel Trenaunay Syndrome, Klippel-Trenaunay-Weber Syndrome, Kluver-Bucy Syndrome, KMS, Kniest Dysplasia,
- 15 Kniest Syndrome, Kobner's Disease, Koebberling-Dunnigan Syndrome, Kohlmeier-Degos Disease, Kok Disease, Korsakoff Psychosis, Korsakoff's Syndrome, Krabbe's Disease Included, Krabbe's Leukodystrophy, Kramer Syndrome, KSS, KSS, KTS, KTW Syndrome, Kufs Disease, Kugelberg-Welander Disease, Kugelberg-Welander Disease, Kugelberg-Welander Syndrome, Kugelberg-Welander Syndrome, Kugelberg-Welander
- 20 Syndrome, Kussmaul-Landry Paralysis, KWS, L-3-Hydroxy-Acyl-CoA Dehydrogenase (LCHAD) Deficiency, Laband Syndrome, Labhart-Willi Syndrome, Labyrinthine Syndrome, Labyrinthine Hydrops, Lacrimo-Auriculo-Dento-Digital Syndrome, Lactase Isolated Intolerance, Lactase Deficiency, Lactation-Uterus Atrophy, Lactic Acidosis Leber Hereditary Optic Neuropathy, Lactic and Pyruvate Acidemia with Carbohydrate
- 25 Sensitivity, Lactic and Pyruvate Acidemia with Episodic Ataxia and Weakness, Lactic and Pyruvate Acidemia with Carbohydrate Sensitivity,Lactic and Pyruvate, Lactic acidosis, Lactose Intolerance of Adulthood, Lactose Intolerance, Lactose Intolerance of Childhood, Lactose Intolerance, LADD Syndrome, LADD, Lafora Disease Included, Lafora Body Disease, Laki-Lorand Factor Deficiency, LAM, Lambert Type Ichthyosis, Lambert-Eaton
- 30 Syndrome, Lambert-Eaton Myasthenic Syndrome, Lamellar Recessive Ichthyosis, Lamellar Recessive Ichthyosis, Lamellar Ichthyosis, Lamellar Recessive Ichthyosis,

- Lancereaux-Mathieu-Weil Spirochetosis, Landau-Kleffner Syndrome, Landouzy Dejérine Muscular Dystrophy, Landry Ascending Paralysis, Langer-Salidino Type Achondroensis (Type II), Langer Giedion Syndrome, Langerhans-Cell Granulomatosis, Langerhans-Cell Histiocytosis (LCH), Large Atrial and Ventricular Defect, Laron Dwarfism, Laron Type  
5 Pituitary Dwarfism, Larsen Syndrome, Laryngeal Dystonia, Latah (Observed in Malaysia), Late Infantile Neuroaxonal Dystrophy, Late Infantile Neuroaxonal Dystrophy, Late Onset Cockayne Syndrome Type III (Type C), Late-Onset Dystonia, Late-Onset Immunoglobulin Deficiency, Late-Onset Immunoglobulin Deficiency, Late Onset Pelizaeus-Merzbacher Brain Sclerosis, Lattice Corneal Dystrophy, Lattice Dystrophy, Launois-Bensaude,  
10 Launois-Cleret Syndrome, Laurence Syndrome, Laurence-Moon Syndrome, Laurence-Moon/Bardet-Biedl, Lawrence-Seip Syndrome, LCA, LCAD Deficiency, LCAD, LCAD, LCAD, LCADH Deficiency, LCH, LCHAD, LCHAD, LCPD, Le Jeune Syndrome, Leband Syndrome, Leber's Amaurosis, Leber's Congenital Amaurosis, Congenital Absence of the Rods and Cones, Leber's Congenital Tapetoretinal Degeneration, Leber's  
15 Congenital Tapetoretinal Dysplasia, Leber's Disease, Leber's Optic Atrophy, Leber's Optic Neuropathy, Left Ventricular Fibrosis, Leg Ulcer, Legg-Calve-Perthes Disease, Leigh's Disease, Leigh's Disease, Leigh's Syndrome, Leigh's Syndrome (Subacute Necrotizing Encephalomyopathy), Leigh Necrotizing Encephalopathy, Lennox-Gastaut Syndrome, Lentigio-Polyposis-Digestive Syndrome, Lentigio-Polyposis-Digestive  
20 Syndrome, Lenz Dysmorphogenetic Syndrome, Lenz Dysplasia, Lenz Microphthalmia Syndrome, Lenz Syndrome, LEOPARD Syndrome, Leprechaunism, Leprechaunism, Leptomeningeal Angiomatosis, Leptospiral Jaundice, Leri-Weill Disease, Leri-Weil Dyschondrosteosis, Leri-Weil Syndrome, Lermoyez Syndrome, Leroy Disease, Lesch Nyhan Syndrome, Lethal Infantile Cardio myopathy, Lethal Neonatal Dwarfism, Lethal  
25 Osteochondrodysplasia, Letterer-Siwe Disease, Leukocytic Anomaly Albinism, Leukocytic Inclusions with Platelet Abnormality, Leukodystrophy, Leukodystrophy with Rosenthal Fibers, Leukoencephalitis Periaxialis Concentric, Levine-Critchley Syndrome, Levulosuria, Levy-Hollister Syndrome, LGMD, LGS, LHON, LHON, LIC, Lichen Ruber Acuminatus, Lichen Acuminatus, Lichen Amyloidosis, Lichen Planus, Lichen Psoriasis,  
30 Lignac-Debre-Fanconi Syndrome, Lignac-Fanconi Syndrome, Ligneous Conjunctivitis, Limb-Girdle Muscular Dystrophy, Limb Girdle Muscular Dystrophy, Limb

- Malformations-Dento-Digital Syndrome, Limit Dextrinosis, Linear Nevoid Hypermelanosis, Linear Nevus Sebaceous Syndrome, Linear Scleroderma, Linear Sebaceous Nevus Sequence, Linear Sebaceous Nevus Syndrome, Lingua Fissurata, Lingua Plicata, Lingua Scrotalis, Linguofacial Dyskinesia, Lip Pseudocleft-hemangiomatous  
5 Branchial Cyst Syndrome, Lipid Granulomatosis, Lipid Histiocytosis, Lipid Kerasin Type, Lipid Storage Disease, Lipid-Storage myopathy Associated with SCAD Deficiency, Lipidosis Ganglioside Infantile, Lipidosis Ganglioside Infantile, Lipoatrophic Diabetes Mellitus, Lipodystrophy, Lipoid Corneal Dystrophy, Lipoid Hyperplasia-Male Pseudohermaphroditism, Lipoid Hyperplasia-Male Pseudohermaphroditism, Lipomatosis  
10 of Pancreas Congenital, Lipomucopolysaccharidosis Type I, Lipomyelomeningocele, Lipoprotein Lipase Deficiency Familial, LIS, LIS1, Lissencephaly 1, Lissencephaly Type I, Lissencephaly variants with agenesis of the corpus callosum cerebellar hypoplasia or other anomalies, Little Disease, Liver Phosphorylase Deficiency, LKS, LM Syndrome, Lobar Atrophy, Lobar Atrophy of the Brain, Lobar Holoprosencephaly, Lobar Tension  
15 Emphysema in Infancy, Lobstein Disease (Type I), Lobster Claw Deformity, Lobster Claw Deformity, Localized Epidermolysis Bullosa, Localized Lipodystrophy, Localized Neuritis of the Shoulder Girdle, Loeffler's Disease, Loeffler Endomyocardial Fibrosis with Eosinophilia, Loeffler Fibroplastic Parietal Endocarditis, Loken Syndrome, Loken-Senior Syndrome, Long-Chain 3-hydroxyacyl-CoA Dehydrogenase (LCHAD), Long Chain Acyl  
20 CoA Dehydrogenase Deficiency, Long-Chain Acyl-CoA Dehydrogenase (ACADL), Long-Chain Acyl-CoA Dehydrogenase Deficiency, Long QT Syndrome without Deafness, Lou Gehrig's Disease, Lou Gehrig's Disease Included, Louis-Bar Syndrome, Low Blood Sugar, Low-Density Beta Lipoprotein Deficiency, Low Imperforate Anus, Low Potassium Syndrome, Lowe syndrome, Lowe's Syndrome, Lowe-Bickel Syndrome, Lowe-Terry-  
25 MacLachlan Syndrome, LS, LS, LTD, Lubs Syndrome, Lubs Syndrome, Luft Disease, Lumbar Canal Stenosis, Lumbar Spinal Stenosis, Lumbosacral Spinal Stenosis, Lundborg-Unverricht Disease, Lundborg-Unverricht Disease Included, Lupus, Lupus, Lupus Erythematosus, Luschka-Magendie Foramina Atresia, Lyell Syndrome, Lyelles Syndrome, Lymphadenoid Goiter, Lymphangiectatic Protein-Losing Enteropathy,  
30 Lymphangioleiomyomatosis, Lymphangioleiomyomatosis, Lymphangiomas, Lymphatic Malformations, Lynch Syndromes, Lynch Syndrome I, Lynch Syndrome II, Lysosomal

- Alpha-N-Acetylgalactosaminidase Deficiency Schindler Type, Lysosomal  
Glycoaminoacid Storage Disease-Angiokeratoma Corporis Diffusum, Lysosomal  
Glucosidase Deficiency, Lysosomal Glucosidase Deficiency, MAA, Machado Disease,  
Machado-Joseph Disease, Macrencephaly, Macrocephaly, Macrocephaly  
5 Hemihypertrophy, Macrocephaly with Multiple Lipomas and Hemangiomata, Macrocephaly with Pseudopapilledema and Multiple Hemangiomata, Macroglobulinemia,  
Macroglossia, Macroglossia-Omphalocele-Visceromegaly Syndrome, Macrostomia  
Ablepheron Syndrome, Macrothrombocytopenia Familial Bernard-Soulier Type, Macula  
Lutea degeneration, Macular Amyloidosis, Macular Degeneration, Macular Degeneration  
10 Disciform, Macular Degeneration Senile, Macular Dystrophy, Macular Type Corneal  
Dystrophy, MAD, MAD, Madelung's Disease, Maffucci Syndrome, Major Epilepsy,  
Malabsorption, Malabsorption-Ectodermal Dysplasia-Nasal Alar Hypoplasia, Maladie de  
Roger, Maladie de Tics, Male Malformation of Limbs and Kidneys, Male Turner  
Syndrome, Malignant Acanthosis, Malignant Acanthosis Nigricans, Malignant  
15 Astrocytoma, Malignant Atrophic Papulosis, Malignant Fever, Malignant  
Hyperphenylalaninemia, Malignant Hyperphenylalaninemia, Malignant Hyperpyrexia,  
Malignant Hyperthermia, Malignant Melanoma, Malignant Tumors of the Central Nervous  
System, Mallory-Weiss Laceration, Mallory-Weiss Tear, Mallory-Weiss Syndrome,  
Mammary Paget's Disease, Mandibular Ameloblastoma, Mandibulofacial Dysostosis,  
20 Mannosidosis, Map-Dot-Fingerprint Type Corneal Dystrophy, Maple Syrup Urine Disease,  
Maple Syrup Urine Disease, Marble Bones, Marchiafava-Micheli Syndrome, Marcus Gunn  
Jaw-Winking Syndrome, Marcus Gunn Phénoménon, Marcus Gunn Ptosis with jaw-  
winking, Marcus Gunn Syndrome, Marcus Gunn (Jaw-Winking) Syndrome, Marcus Gunn  
Ptosis (with jaw-winking), Marden-Walker Syndrome, Marden-Walker Type Connective  
25 Tissue Disorder, Marfan's Abiotrophy, Marfan-Achard syndrome, Marfan Syndrome,  
Marfan Syndrome, Marfan's Syndrome I, Marfan's Variant, Marfan-Achard syndrome,  
Marfanoid Hypermobility Syndrome, Marginal Corneal Dystrophy, Marie's Ataxia,  
Marie's Ataxia, Marie Disease, Marie-Sainton Disease, Marie Strumpell Disease, Marie-  
Strumpell Spondylitis, Marinesco-Sjögren Syndrome, Marinesco-Sjögren-Gorland  
30 Syndrome, Marker X Syndrome, Maroteaux Lamy Syndrome, Maroteaux Type  
Acromesomelic Dysplasia, Marshall's Ectodermal Dysplasias With Ocular and Hearing

- Defects, Marshall-Smith Syndrome, Marshall Syndrome, Marshall Type Deafness-Myopia-Cataract-Saddle Nose, Martin-Albright Syndrome, Martin-Bell Syndrome, Martorell Syndrome, MASA Syndrome, Massive Myoclonia, Mast Cell Leukemia, Mastocytosis, Mastocytosis With an Associated Hematologic Disorder, Maumenee  
5 Corneal Dystrophy, Maxillary Ameloblastoma, Maxillofacial Dysostosis, Maxillonasal Dysplasia, Maxillonasal Dysplasia Binder Type, Maxillopalpebral Synkinesis, May-Hegglin Anomaly, MCAD Deficiency, MCAD, MCAD, MCAD, McArdle Disease, McCune-Albright, MCD, McKusick Type Metaphyseal Chondrodysplasia, McKusick Type Metaphyseal Chondrodysplasia, MCR, MCTD, Meckel Syndrome, Meckel-Gruber  
10 Syndrome, Median Cleft Face Syndrome, Mediterranean Anemia, Medium-Chain Acyl-CoA dehydrogenase (ACADM), Medium Chain Acyl-CoA Dehydrogenase (MCAD) Deficiency, Medium-Chain Acyl-CoA Dehydrogenase Deficiency, Medium Chain Acyl CoA Dehydrogenase Deficiency, Medullary Cystic Disease, Medullary Cystic Disease, Medullary Sponge Kidney, MEF, Megaesophagus, Megalencephaly, Megalencephaly with  
15 Hyaline Inclusion, Megalencephaly with Hyaline Panneuropathy, Megaloblastic Anemia, Megaloblastic Anemia of Pregnancy, Megalocornea-Mental Retardation Syndrome, Meier-Gorlin Syndrome, Meige's Lymphedema, Meige's Syndrome, Melanodermic Leukodystrophy, Melanoplakia-Intestinal Polyposis, Melanoplakia-Intestinal Polyposis, MELAS Syndrome, MELAS, Melkersson Syndrome, Melnick-Fraser Syndrome, Melnick-  
20 Needles Osteodysplasty, Melnick-Needles Syndrome, Membranous Lipodystrophy, Mendes Da Costa Syndrome, Meniere Disease, Ménière's Disease, Meningeal Capillary Angiomatosis, Menkes Disease, Menke's Syndrome I, Mental Retardation Aphasia Shuffling Gait Adducted Thumbs (MASA), Mental Retardation-Deafness-Skeletal Abnormalities-Coarse Face with Full Lips, Mental Retardation with Hypoplastic 5th  
25 Fingernails and Toenails, Mental Retardation with Osteocartilaginous Abnormalities, Mental Retradation-X-linked with Growth Delay-Deafness-Microgenitalism, Menzel Type OPCA, Mermaid Syndrome, MERRF, MERRF Syndrome, MERRF, Merten-Singleton Syndrome, MES, Mesangial IGA Nephropathy, Mesenteric Lipodystrophy, Mesiodens-Cataract Syndrome, Mesodermal Dysmorphodystrophy, Mesomelic Dwarfism-Madelung  
30 Deformity, Metabolic Acidosis, Metachromatic Leukodystrophy, Metatarsus Varus, Metatropic Dwarfism Syndrome, Metatropic Dysplasia, Metatropic Dysplasia I,

- Metatropic Dysplasia II, Methylmalonic Acidemia, Methylmalonic Aciduria, Meulengracht's Disease, MFD1, MG, MH, MHA, Micrencephaly, Microcephalic Primordial Dwarfism I, Microcephaly, Microcephaly-Hiatal Hernia-Nephrosis Galloway Type, Microcephaly-Hiatal Hernia-Nephrotic Syndrome, Microcystic Corneal Dystrophy,
- 5 Microcythemia, Microlissencephaly, Microphthalmia, Microphthalmia, Microphthalmia or Anophthalmos with Associated Anomalies, Micropolygyria With Muscular Dystrophy, Microtia Absent Patellae Micrognathia Syndrome, Microvillus Inclusion Disease, MID, Midsystolic-click-late systolic murmur syndrome, Miescher's Type I Syndrome, Mikulicz Syndrome, Mikulicz-Radecki Syndrome, Mikulicz-Sjogren Syndrome, Mild Autosomal
- 10 Recessive, Mild Intermediate Maple Syrup Urine Disease, Mild Maple Syrup Urine Disease, Miller Syndrome, Miller-Dieker Syndrome, Miller-Fisher Syndrome, Milroy Disease, Minkowski-Chauffard Syndrome, Minor Epilepsy, Minot-Von Willebrand Disease, Mirror-Image Dextrocardia, Mitochondrial Beta-Oxidation Disorders, Mitochondrial and Cytosolic, Mitochondrial Cytopathy, Mitochondrial Cytopathy, Kearn-
- 15 Sayre Type, Mitochondrial Encephalopathy, Mitochondrial Encephalo myopathy Lactic Acidosis and Strokelike Episodes, Mitochondrial myopathy, Mitochondrial myopathy Encephalopathy Lactic Acidosis Stroke-Like Episode, Mitochondrial PEPCK Deficiency, Mitral-valve prolapse, Mixed Apnea, Mixed Connective Tissue Disease, Mixed Connective Tissue Disease, Mixed Hepatic Porphyria, Mixed Non-Fluent Aphasia, Mixed
- 20 Sleep Apnea, Mixed Tonic and Clonic Torticollis, MJD, MKS, ML I, ML II, ML II, ML III, ML IV, ML Disorder Type I, ML Disorder Type II, ML Disorder Type III, ML Disorder Type IV, MLNS, MMR Syndrome, MND, MNGIE, MNS, Mobitz I, Mobitz II, Mobius Syndrome, Moebius Syndrome, Moersch-Woltmann Syndrome, Mohr Syndrome, Monilethrix, Monomodal Visual Amnesia, Mononeuritis Multiplex, Mononeuritis
- 25 Peripheral, Mononeuropathy Peripheral, Monosomy 3p2, Monosomy 9p Partial, Monosomy 11q Partial, Monosomy 13q Partial, Monosomy 18q Syndrome, Monosomy X, Monostotic Fibrous Dysplasia, Morgagni-Turner-Albright Syndrome, Morphea, Morquio Disease, Morquio Syndrome, Morquio Syndrome A, Morquio Syndrome B, Morquio-Braillsford Syndrome, Morvan Disease, Mosaic Tetrasomy 9p, Motor Neuron Disease,
- 30 Motor Neuron Disease, Motor Neuron Syndrome, Motor Neurone Disease, Motoneuron Disease, Motoneurone Disease, Motor System Disease (Focal and Slow), Moya-moya

- Disease, Moyamoya Disease, MPS, MPS I, MPS I H, MPS I H/S Hurler/Scheie Syndrome, MPS I S Scheie Syndrome, MPS II, MPS IIA, MPS IIB, MPS II-AR Autosomal Recessive Hunter Syndrome, MPS II-XR, MPS II-XR Severe Autosomal Recessive, MPS III, MPS III A B C and D Sanfilippo A, MPS IV, MPS IV A and B
- 5 Morquio A, MPS V, MPS VI, MPS VI Severe Intermediate Mild Maroteaux-Lamy, MPS VII, MPS VII Sly Syndrome, MPS VIII, MPS Disorder, MPS Disorder I, MPS Disorder II, MPS Disorder III, MPS Disorder VI, MPS Disorder Type VII, MRS, MS, MSA, MSD, MSL, MSS, MSUD, MSUD, MSUD Type Ib, MSUD Type II, Mucocutaneous Lymph Node Syndrome, Mucolipidosis I, Mucolipidosis II, Mucolipidosis II, Mucolipidosis III,
- 10 Mucolipidosis IV, Mucopolysaccharidosis, Mucopolysaccharidosis I-H, Mucopolysaccharidosis I-S, Mucopolysaccharidosis II, Mucopolysaccharidosis III, Mucopolysaccharidosis IV, Mucopolysaccharidosis VI, Mucopolysaccharidosis VII, Mucopolysaccharidosis Type I, Mucopolysaccharidosis Type II, Mucopolysaccharidosis Type III, Mucopolysaccharidosis Type VII, Mucosis, Mucosulfatidosis, Mucous Colitis,
- 15 Mucoviscidosis, Mulibrey Dwarfism, Mulibrey Nanism Syndrome, Mullerian Duct Aplasia-Renal Aplasia-Cervicothoracic Somite Dysplasia, Mullerian Duct-Renal-Cervicothoracic-Upper Limb Defects, Mullerian Duct and Renal Agenesis with Upper Limb and Rib Anomalies, Mullerian-Renal-Cervicothoracic Somite Abnormalities, Multi-Infarct Dementia Binswanger's Type, Multicentric Castleman's Disease, Multifocal
- 20 Eosinophilic Granuloma, Multiple Acyl-CoA Dehydrogenase Deficiency, Multiple Acyl-CoA Dehydrogenase Deficiency, Multiple Acyl-CoA Dehydrogenase Deficiency / Glutaric Aciduria Type II, Multiple Angiomas and Endochondromas, Multiple Carboxylase Deficiency, Multiple Cartilaginous Enchondroses, Multiple Cartilaginous Exostoses, Multiple Enchondromatosis, Multiple Endocrine Deficiency Syndrome Type II, Multiple
- 25 Epiphyseal Dysplasia, Multiple Exostoses, Multiple Exostoses Syndrome, Multiple Familial Polyposis, Multiple Lentigines Syndrome, Multiple Myeloma, Multiple Neuritis of the Shoulder Girdle, Multiple Osteochondromatosis, Multiple Peripheral Neuritis, Multiple Polyposis of the Colon, Multiple Pterygium Syndrome, Multiple Sclerosis, Multiple Sclerosis, Multiple Sulfatase Deficiency, Multiple Symmetric Lipomatosis,
- 30 Multiple System Atrophy, Multisynostotic Osteodysgenesis, Multisynostotic Osteodysgenesis with Long Bone Fractures, Mulvihill-Smith Syndrome, MURCS

- Association, Murk Jansen Type Metaphyseal Chondrodysplasia, Muscle Carnitine Deficiency, Muscle Core Disease, Muscle Phosphofructokinase Deficiency, Muscular Central Core Disease, Muscular Dystrophy, Muscular Dystrophy Classic X-linked Recessive, Muscular Dystrophy Congenital With Central Nervous System Involvement,
- 5 Muscular Dystrophy Congenital Progressive with Mental Retardation, Muscular Dystrophy Facioscapulohumeral, Muscular Rheumatism, Muscular Rigidity - Progressive Spasm, Musculoskeletal Pain Syndrome, Mutilating Acropathy, Mutilating Acropathy, Mutism, mvp, MVP, MWS, Myasthenia Gravis, Myasthenia Gravis, Myasthenia Gravis Pseudoparalytica, Myasthenic Syndrome of Lambert-Eaton, Myelinoclastic Diffuse
- 10 Sclerosis, Myelomatosis, Myhre Syndrome, Myoclonic Astatic Petit Mal Epilepsy, Myoclonic Dystonia, Myoclonic Encephalopathy of Infants, Myoclonic Epilepsy, Myoclonic Epilepsy Hartung Type, Myoclonus Epilepsy Associated with Ragged Red Fibers, Myoclonic Epilepsy and Ragged-Red Fiber Disease, Myoclonic Progressive Familial Epilepsy, Myoclonic Progressice Familial Epilepsy, Myoclonic Seizure,
- 15 Myoclonus, Myoclonus Epilepsy, Myoencephalopathy Ragged-Red Fiber Disease, Myofibromatosis, Myofibromatosis Congenital, Myogenic Facio-Scapulo-Peroneal Syndrome, Myoneurogastrointestinal Disorder and Encephalopathy, Myopathic Arthrogryposis Multiplex Congenita, Myopathic Carnitine Deficiency, myopathy Central Fibrillar, myopathy Congenital Nonprogressive, myopathy Congenital Nonprogressive
- 20 with Central Axis, myopathy with Deficiency of Carnitine Palmitoyltransferase, myopathy-Marinesco-Sjogren Syndrome, myopathy-Metabolic Carnitine Palmitoyltransferase Deficiency, myopathy Mitochondrial-Encephalopathy-Lactic Acidosis-Stroke, myopathy with Sarcoplasmic Bodies and Intermediate Filaments, Myophosphorylase Deficiency, Myositis Ossificans Progressiv, Myotonia Atrophica,
- 25 Myotonia Congenita, Myotonia Congenita Intermittens, Myotonic Dystrophy, Myotonic myopathy Dwarfism Chondrodystrophy Ocular and Facial Anomalies, Myotubular myopathy, Myotubular myopathy X-linked, Myproic Acid, Myriachit (Observed in Siberia), Myxedema, N-Acetylglucosamine-1-Phosphotransferase Deficiency, N-Acetyl Glutamate Synthetase Deficiency, NADH-CoQ reductasedeficiency, Naegeli Ectodermal
- 30 Dysplasias, Nager Syndrome, Nager Acrofacial Dysostosis Syndrome, Nager Acrofacial Dysostosis Syndrome, Nager Syndrome, NAGS Deficiency, Nail Dystrophy-Deafness

- Syndrome, Nail Dysgenesis and Hypodontia, Nail-Patella Syndrome, Nance-Horan Syndrome, Nanocephalic Dwarfism, Nanocephaly, Nanophthalmia, Narcolepsy, Narcoleptic syndrome, NARP, Nasal-fronto-faciodysplasia, Nasal Alar Hypoplasia Hypothyroidism Pancreatic Achylia Congenital Deafness, Nasomaxillary Hypoplasia,
- 5 Nasu Lipodystrophy, NBIA1, ND, NDI, NDP, Necrotizing Encephalomyopathy of Leigh's, Necrotizing Respiratory Granulomatosis, Neill-Dingwall Syndrome, Nelson Syndrome, Nemaline myopathy, Neonatal Adrenoleukodystrophy, Neonatal Adrenoleukodystrophy (NALD), Neonatal Adrenoleukodystrophy (ALD), Neonatal Autosomal Recessive Polycystic Kidney Disease, Neonatal Dwarfism, Neonatal Hepatitis,
- 10 Neonatal Hypoglycemia, Neonatal Lactose Intolerance, Neonatal Lymphedema due to Exudative Enteropathy, Neonatal Progeroid Syndrome, Neonatal Pseudo-Hydrocephalic Progeroid Syndrome of Wiedemann-Rautenstrauch, Neoplastic Arachnoiditis, Nephroblastom, Nephrogenic Diabetes Insipidus, Nephronophthisis Familial Juvenile, Nephronophthisis Familial Juvenile, Nephropathic Cystinosis, Nephropathy-
- 15 Pseudohermaphroditism-Wilms Tumor, Nephrosis-Microcephaly Syndrome, Nephrosis-Neuronal Dysmigration Syndrome, Nephrotic-Glycosuric-Dwarfism-Rickets-Hypophosphatemic Syndrome, Netherton Disease, Netherton Syndrome, Netherton Syndrome Ichthyosis, Nettleship Falls Syndrome (X-Linked), Neu-Laxova Syndrome, Neuhauser Syndrome, Neural-tube defects, Neuralgic Amyotrophy, Neuralgic
- 20 Amyotrophy, Neuraminidase Deficiency, Neuracutaneous melanosis, Neurinoma of the Acoustic Nerve, Neurinoma, Neuroacanthocytosis, Neuroaxonal Dystrophy Schindler Type, Neurodegeneration with brain iron accumulation type 1 (NBIA1), Neurofibroma of the Acoustic Nerve, Neurogenic Arthrogryposis Multiplex Congenita, Neuromyelitis Optica, Neuromyotonia, Neuromyotonia, Focal, Neuromyotonia, Generalized, Familial,
- 25 Neuromyotonia, Generalized,Sporadic, Neuronal Axonal Dystrophy Schindler Type, Neuronal Ceroid Lipofuscinosis Adult Type, Neuronal Ceroid Lipofuscinosis Juvenile Type, Neuronal Ceroid Lipofuscinosis Type 1, Neuronopathic Acute Gaucher Disease, Neuropathic Amyloidosis, Neuropathic Beriberi, Neuropathy Ataxia and Retinitis Pigmentosa, Neuropathy of Brachialplexus Syndrome, Neuropathy Hereditary Sensory
- 30 Type I, Neuropathy Hereditary Sensory Type II, Neutral Lipid Storage Disease, Nevii, Nevous Basal Cell Carcinoma Syndrome, Nevus, Nevus Cavernosus, Nevus Comedonicus,

- Nevus Depigmentosus, Nevus Sebaceous of Jadassohn, Nezelof's Syndrome, Nezelof's Thymic Aplasia, Nezelof Type Severe Combined Immunodeficiency, NF, NF1, NF2, NF-1, NF-2, NHS, Niemann Pick Disease, Nieman Pick disease Type A (acute neuronopathic form), Nieman Pick disease Type B, Nieman Pick Disease Type C (chronic neuronopathic form), Nieman Pick disease Type D (Nova Scotia variant), Nieman Pick disease Type E, Nieman Pick disease Type F (sea-blue histiocyte disease), Night Blindness, Nigrospinodental Degeneration, Niikawakuroki Syndrome, NLS, NM, Noack Syndrome Type I, Nocturnal Myoclonus Hereditary Essential Myoclonus, Nodular Cornea Degeneration, Non-Bullous CIE, Non-Bullous Congenital Ichthyosiform Erythroderma,
- 5 Non-Communicating Hydrocephalus, Non-Deletion Type Alpha-Thalassemia / Mental Retardation syndrome, Non-Ketotic Hyperglycinemia Type I (NKHI), Non-Ketotic Hyperglycinemia, Non-Lipid Reticuloendotheliosis, Non-Neuronopathic Chronic Adult Gaucher Disease, Non-Scarring Epidermolysis Bullosa, Nonarteriosclerotic Cerebral Calcifications, Nonarticular Rheumatism, Noncerebral Juvenile Gaucher Disease,
- 10 Nondiabetic Glycosuria, Nonischemic Cardiomyopathy, Nonketotic Hypoglycemia and Carnitine Deficiency due to MCAD Deficiency, Nonketotic Hypoglycemia Caused by Deficiency of Acyl-CoA Dehydrogenase, Nonketotic Glycinemia, Nonne's Syndrome, Nonne-Milroy-Meige Syndrome, Nonopalescent Opalescent Dentine, Nonpuerperal Galactorrhea-Amenorrhea, Nonsecretory Myeloma, Nonspherocytic Hemolytic Anemia,
- 15 20 Nontropical Sprue, Noonan Syndrome, Norepinephrine, Normal Pressure Hydrocephalus, Norman-Roberts Syndrome, Norrbottian Gaucher Disease, Norrie Disease, Norwegian Type Hereditary Cholestasis, NPD, NPS, NS, NSA, Nuchal Dystonia Dementia Syndrome, Nutritional Neuropathy, Nyhan Syndrome, OAV Spectrum, Obstructive Apnea, Obstructive Hydrocephalus, Obstructive Sleep Apnea, OCC Syndrome, Occlusive Thromboangiopathy, OCCS, Occult Intracranial Vascular Malformations, Occult Spinal Dysraphism Sequence, Ochoa Syndrome, Ochronosis, Ochronotic Arthritis, OCR, OCRL, Octocephaly, Ocular Albinism, Ocular Herpes, Ocular Myasthenia Gravis, Oculo-Auriculo-Vertebral Dysplasia, Oculo-Auriculo-Vertebral Spectrum, Oculo-Bucco-Genital Syndrome, Oculocerebral Syndrome with Hypopigmentation, Oculocerebrocutaneous
- 25 30 Syndrome, Oculo-Cerebro-Renal, Oculocerebrorenal Dystrophy, Oculocerebrorenal Syndrome, Oculocraniosomatic Syndrome (obsolete), Oculocutaneous Albinism,

- Oculocutaneous Albinism Chediak-Higashi Type, Oculo-Dento-Digital Dysplasia, Oculo-Dento-Digital Dysplasia, Oculodentodigital Syndrome, Oculo-Dento-Osseous Dysplasia, Oculo-Dento-Osseous Dysplasia, Oculo Gastrointestinal Muscular Dystrophy, Oculo Gastrointestinal Muscular Dystrophy, Oculogastrointestinal Muscular Dystrophy,
- 5 Oculomandibulodyscephaly with hypotrichosis, Oculomandibulofacial Syndrome, Oculomotor with Congenital Contractures and Muscle Atrophy, Oculosympathetic Palsy, ODD Syndrome, ODD Syndrome, ODOD, Odontogenic Tumor, Odontotrichomelic Syndrome, OFD, OFD Syndrome, Ohio Type Amyloidosis (Type VII), OI, OI Congenita, OI Tarda, Oldfield Syndrome, Oligohydramnios Sequence, Oligophrenia Microphthalmos,
- 10 Oligophrenic Polydystrophy, Olivopontocerebellar Atrophy, Olivopontocerebellar Atrophy, Olivopontocerebellar Atrophy with Dementia and Extrapiramidal Signs, Olivopontocerebellar Atrophy with Retinal Degeneration, Olivopontocerebellar Atrophy I, Olivopontocerebellar Atrophy II, Olivopontocerebellar Atrophy III, Olivopontocerebellar Atrophy IV, Olivopontocerebellar Atrophy V, Ollier Disease, Ollier Osteochondromatosis,
- 15 Omphalocele-Visceromegaly-Macroglossia Syndrome, Ondine's Curse, Onion-Bulb Neuropathy, Onion Bulb Polyneuropathy, Onychoosteodysplasia, Onychotrichodysplasia with Neutropenia, OPCA, OPCA I, OPCA II, OPCA III, OPCA IV, OPCA V, OPD Syndrome, OPD Syndrome Type I, OPD Syndrome Type II, OPD I Syndrome, OPD II Syndrome, Ophthalmoarthropathy, Ophthalmoplegia-Intestinal Pseudoobstruction,
- 20 Ophthalmoplegia, Pigmentary Degeneration of the Retina and Cadio myopathy, Ophthalmoplegia Plus Syndrome, Ophthalmoplegia Syndrome, Opitz BBB Syndrome, Opitz BBB/G Compound Syndrome, Opitz BBBG Syndrome, Opitz-Frias Syndrome, Opitz G Syndrome, Opitz G/BBB Syndrome, Opitz Hypertelorism-Hypospadias Syndrome, Opitz-Kaveggia Syndrome, Opitz Oculogenitotaryngeal Syndrome, Opitz
- 25 Trigonocephaly Syndrome, Opitz Syndrome, Opsoclonus, Opsoclonus-Myoclonus, Ophthalmoneuromyelitis, Optic Atrophy Polyneuropathy and Deafness, Optic Neuroencephalomyopathy, Optic Neuromyelitis, Opticomylitis, Optochiasmatic Arachnoiditis, Oral-Facial Clefts, Oral-facial Dyskinesia, Oral Facial Dystonia, Oral-Facial-Digital Syndrome, Oral-Facial-Digital Syndrome Type I, Oral-Facial-Digital Syndrome I, Oral-Facial-Digital Syndrome II, Oral-Facial-Digital Syndrome III, Oral-Facial-Digital Syndrome IV, Orbital Cyst with Cerebral and Focal Dermal Malformations,
- 30

- Ornithine Carbamyl Transferase Deficiency, Ornithine Transcarbamylase Deficiency, Orocraniodigital Syndrome, Orofaciodigital Syndrome, Oromandibular Dystonia, Orthostatic Hypotension, Osler-Weber-Rendu disease, Osseous-Oculo-Dento Dysplasia, Osseous-Oculo-Dento Dysplasia, Osteitis deformans, Osteochondrodystrophy Deformans,
- 5 Osteochondroplasia, Osteodysplasty of Melnick and Needles, Osteogenesis Imperfect, Osteogenesis Imperfecta, Osteogenesis Imperfecta Congenita, Osteogenesis Imperfecta Tarda, Osteohypertrophic Nevus Flammeus, Osteopathia Hyperostotica Scleroticans Multiplex Infantalis, Osteopathia Hyperostotica Scleroticans Multiplex Infantalis, Osteopathyrosis, Osteopetrosis, Osteopetrosis Autosomal Dominant Adult Type,
- 10 Osteopetrosis Autosomal Recessive Malignant Infantile Type, Osteopetrosis Mild Autosomal Recessive Intermediate Typ, Osteosclerosis Fragilis Generalisata, Osteosclerotic Myeloma, Ostium Primum Defect (endocardial cushion defects included), Ostium Secundum Defect, OTC Deficiency, Oto Palato Digital Syndrome, Oto-Palato-Digital Syndrome Type I, Oto-Palatal-Digital Syndrome Type II, Otodental Dysplasia,
- 15 Otopalatodigital Syndrome, Otopalataldigital Syndrome Type II, Oudtshoorn Skin, Ovarian Dwarfism Turner Type, Ovary Aplasia Turner Type, OWR, Oxalosis, Oxidase deficiency, Oxycephaly, Oxycephaly, Oxycephaly-Acrocephaly, P-V, PA, PAC, Pachyonychia Ichtyosiforme, Pachyonychia Congenita with Natal Teeth, Pachyonychia Congenita, Pachyonychia Congenita Keratosis Disseminata Circumscripta (follicularis),
- 20 Pachyonychia Congenita Jadassohn-Lewandowsky Type, PAF with MSA, Paget's Disease, Paget's Disease of Bone, Paget's Disease of the Breast, Paget's Disease of the Nipple, Paget's Disease of the Nipple and Areola, Pagon Syndrome, Painful Ophthalmoplegia, PAIS, Palatal Myoclonus, Palato-Oto-Digital Syndrome, Palatal-Oto-Digital Syndrome Type I, Palatal-Oto-Digital SyndromeType II, Pallister Syndrome, Pallister-Hall
- 25 Syndrome, Pallister-Killian Mosaic Syndrome, Pallister Mosaic Aneuploidy, Pallister Mosaic Syndrome, Pallister Mosaic Syndrome Tetrasomy 12p, Pallister-W Syndrome, Palmoplantar Hyperkeratosis and Alopecia, Palsy, Pancreatic Fibrosis, Pancreatic Insufficiency and Bone Marrow Dysfunction, Pancreatic Ulcerogenic Tumor Syndrome, Panmyelophthisis, Panmyelopathy, Pantothenate kinase associated neurodegeneration (PKAN), Papillon-Lefevre Syndrome, Papillotonic Psuedotabes, Paralysis Periodica Paramyotonica, Paralytic Beriberi, Paralytic Brachial Neuritis, Paramedian Lower Lip Pits-

- Popliteal Pyerygium Syndrome, Paramedian Diencephalic Syndrome, Paramyeloidosis,  
Paramyoclonus Multiple, Paramyotonia Congenita, Paramyotonia Congenita of Von  
Eulenburg, Parkinson's disease, Paroxysmal Atrial Tachycardia, Paroxysmal Cold  
Hemoglobinuria, Paroxysmal Dystonia, Paroxysmal Dystonia Chorea-thetosis, Paroxysmal  
5 Kinesigenic Dystonia, Paroxysmal Nocturnal Hemoglobinuria, Paroxysmal Normal  
Hemoglobinuria, Paroxysmal Sleep, Parrot Syndrome, Parry Disease, Parry-Romberg  
Syndrome, Parsonage-Turner Syndrome, Partial Androgen Insensitivity Syndrome, Partial  
Deletion of the Short Arm of Chromosome 4, Partial Deletion of the Short Arm of  
Chromosome 5, Partial Deletion of Short Arm of Chromosome 9, Partial Duplication 3q  
10 Syndrome, Partial Duplication 15q Syndrome, Partial Facial Palsy With Urinary  
Abnormalities, Partial Gigantism of Hands and Feet- Nevi-Hemihypertrophy-  
Macrocephaly, Partial Lipodystrophy, Partial Monosomy of Long Arm of Chromosome  
11, Partial Monosomy of the Long Arm of Chromosome 13, Partial Spinal Sensory  
Syndrome, Partial Trisomy 11q, Partington Syndrome, PAT, Patent Ductus Arteriosus,  
15 Pathological Myoclonus, Pauciarticular-Onset Juvenile Arthritis, Pauciarticular-Onset  
Juvenile Arthritis, Paulitis, PBC, PBS, PC Deficiency, PC Deficiency Group A, PC  
Deficiency Group B, PC, Eulenburg Disease, PCC Deficiency, PCH, PCLD, PCT, PD,  
PDA, PDH Deficiency, PDH Deficiency, Pearson Syndrome Pyruvate Carboxylase  
Deficiency, Pediatric Obstructive Sleep Apnea, Peeling Skin Syndrome, Pelizaeus-  
20 Merzbacher Disease, Pelizaeus-Merzbacher Brain Sclerosis, Pelizaeus-Merzbacher Brain  
Sclerosis, Pellagra-Cerebellar Ataxia-Renal Aminoaciduria Syndrome, Pelvic Pain  
Syndrome, Pemphigus Vulgaris, Pena Shokeir II Syndrome, Pena Shokeir Syndrome Type  
II, Penile Fibromatosis, Penile Fibrosis, Penile Induration, Penta X Syndrome, Pentalogy  
of Cantrell, Pentalogy Syndrome, Pentasomy X, PEPCK Deficiency, Pepper Syndrome,  
25 Perheentupa Syndrome, Periarticular Fibrosis, Pericardial Constriction with Growth  
Failure, Pericollagen Amyloidosis, Perinatal Polycystic Kidney Diseases, Perineal Anus,  
Periodic Amyloid Syndrome, Periodic Peritonitis Syndrome, Periodic Somnolence and  
Morbid Hunger, Periodic Syndrome, Peripheral Cystoid Degeneration of the Retina,  
Peripheral Dysostosis-Nasal Hypoplasia-Mental Retardation, Peripheral Neuritis,  
30 Peripheral Neuropathy, Peritoneopericardial Diaphragmatic Hernia, Pernicious Anemia,  
Pernicious Anemia, Pernicious Anemia, Peromelia with Micrognathia, Peroneal Muscular

- Atrophy, Peroneal Nerve Palsy, Peroutka Sneeze, Peroxisomal Acyl-CoA Oxidase, Peroxisomal Beta-Oxidation Disorders, Peroxisomal Bifunctional Enzyme, Peroxisomal Thiolase, Peroxisomal Thiolase Deficiency, Persistent Truncus Arteriosus, Perthes Disease, Petit Mal Epilepsy, Petit Mal Variant, Peutz-Jeghers Syndrome, Peutz-Jeghers  
5 Syndrome, Peutz-Touraine Syndrome, Peutz-Touraine Syndrome, Peyronie Disease, Pfeiffer, Pfeiffer Syndrome Type I, PGA I, PGA II, PGA II, PGA III, PGK, PH Type I, PH Type I, Pharyngeal Pouch Syndrome, PHD Short-Chain Acyl-CoA Dehydrogenase Deficiency, Phenylalanine Hydroxylase Deficiency, Phenylalaninemia, Phenylketonuria, Phenylketonuria, Phenylpyruvic Oligophrenia, Phocomelia, Phocomelia Syndrome,  
10 Phosphoenolpyruvate Carboxykinase Deficiency, Phosphofructokinase Deficiency, Phosphoglycerate Kinase Deficiency, Phosphoglycerokinase, Phosphorylase 6 Kinase Deficiency, Phosphorylase Deficiency Glycogen Storage Disease, Phosphorylase Kinase Deficiency of Liver, Photic Sneeze Reflex, Photic Sneezing, Phototherapeutic keratectomy, PHS, Physicist John Dalton, Phytanic Acid Storage Disease, Pi Phenotype  
15 ZZ, PI, Pick Disease of the Brain, Pick's Disease, Pick's Disease, Pickwickian Syndrome, Pierre Robin Anomaly, Pierre Robin Complex, Pierre Robin Sequence, Pierre Robin Syndrome, Pierre Robin Syndrome with Hyperphalangy and Clinodactyly, Pierre-Marie's Disease, Pigmentary Degeneration of Globus Pallidus Substantia Nigra Red Nucleus, Pili Torti and Nerve Deafness, Pili Torti-Sensorineural Hearing Loss, Pituitary Dwarfism II,  
20 Pituitary Tumor after Adrenalectomy, Pityriasis Pilaris, Pityriasis Rubra Pilaris, PJS, PJS, PKAN, PKD, PKD, PKD1, PKD2, PKD3, PKU, PKU, PKU1, Plagiocephaly, Plagiocephaly, Plagiocephaly, Plasma Cell Myeloma, Plasma Cell Leukemia, Plasma Thromboplastin Component Deficiency, Plasma Transglutaminase Deficiency, Plastic Induration Corpora Cavernosa, Plastic Induration of the Penis, PLD, Plicated Tongue,  
25 PLS, PMD, Pneumorenal Syndrome, PNH, PNM, PNP Deficiency, POD, POH, Poikiloderma Atrophicans and Cataract, Poikiloderma Congenitale, Poland Anomaly, Poland Sequence, Poland Syndactyly, Poland Syndrome, Poliodystrophia Cerebri Progressiva, Polyarthritis Enterica, Polyarteritis Nodosus, Polyarticular-Onset Juvenile Arthritis Type I, Polyarticular-Onset Juvenile Arthritis Type II, Polyarticular-Onset  
30 Juvenile Arthritis Types I and II, Polychondritis, Polycystic Kidney Disease, Polycystic Kidney Disease Medullary Type, Polycystic Kidney Disease Medullary Type, Polycystic

- Liver Disease, Polycystic Ovary Disease, Polycystic Renal Diseases, Polydactyly-Joubert Syndrome, Polydysplastic Epidermolysis Bullosa, Polydystrophia Oligophrenia, Polydystrophic Dwarfism, Polyglandular Autoimmune Syndrome Type III, Polyglandular Autoimmune Syndrome Type II, Polyglandular Autoimmune Syndrome Type I,  
5 Polyglandular Autoimmune Syndrome Type II, Polyglandular Deficiency Syndrome Type II, Polyglandular Syndromes, Polymorphic Macula Lutea Degeneration, Polymorphic Macular Degeneration, Polymorphism of Platelet Glycoprotein Ib, Polymorphous Corneal Dystrophy Hereditary, Polymyalgia Rheumatica, Polymyalgia Rheumatica, Polymyositis and Dermatomyositis, Primary Agammaglobulinemia, Polyneuritis Peripheral,  
10 Polyneuropathy-Deafness-Optic Atrophy, Polyneuropathy Peripheral, Polyneuropathy and Polyradiculoneuropathy, Polyostotic Fibrous Dysplasia, Polyostotic Sclerosing Histiocytosis, Polyposis Familial, Polyposis Gardner Type, Polyposis Hamartomatous Intestinal, Polyposis Hamartomatous Intestinal, Polyposis-Osteomatoses-Epidermoid Cyst Syndrome, Polyposis Skin Pigmentation Alopecia and Fingernail Changes, Polyps and  
15 Spots Syndrome, Polyps and Spots Syndrome, Polyserositis Recurrent, Polysomy Y, Polysyndactyly with Peculiar Skull Shape, Polysyndactyly-Dysmorphic Craniofacies Greig Type, Pompe Disease, Pompe Disease, Popliteal Pterygium Syndrome, Porcupine Man, Porencephaly, Porencephaly, Porphobilinogen deaminase (PBG-D), Porphyria, Porphyria Acute Intermittant, Porphyria Acute Intermittent, Porphyria ALA-D, Porphyria Cutanea  
20 Tarda, Porphyria Cutanea Tarda, Porphyria Cutanea Tarda Hereditaria, Porphyria Cutanea Tarda Symptomatica, Porphyria Hepatica Variegate, Porphyria Swedish Type, Porphyria Variegate, Porphyriam Acute Intermittent, Porphyriins, Porrigo Decalvans, Port Wine Stains, Portuguese Type Amyloidosis, Post-Infective Polyneuritis, Postanoxic Intention Myoclonus, Postaxial Acrofacial Dysostosis, Postaxial Polydactyly, Postencephalitic  
25 Intention Myoclonus, Posterior Corneal Dystrophy Hereditary, Posterior Thalamic Syndrome, Postmyelographic Arachnoiditis, Postnatal Cerebral Palsy, Postoperative Cholestasis, Postpartum Galactorrhea-Amenorrhea Syndrome, Postpartum Hypopituitarism, Postpartum Panhypopituitary Syndrome, Postpartum Panhypopituitarism, Postpartum Pituitary Necrosis, Postural Hypotension, Potassium-Losing Nephritis,  
30 Potassium Loss Syndrome, Potter Type I Infantile Polycystic Kidney Diseases, Potter Type III Polycystic Kidney Disease, PPH, PPS, Prader-Willi Syndrome, Prader-Labhart-Willi

- Fancone Syndrome, Prealbumin Tyr-77 Amyloidosis, Preexcitation Syndrome, Preexcitation Syndrome, Pregnenolone Deficiency, Premature Atrial Contractions, Premature Senility Syndrome, Premature Supraventricular Contractions, Premature Ventricular Complexes, Prenatal or Connatal Neuroaxonal Dystrophy, Presenile Dementia,
- 5 Presenile Macula Lutea Retinae Degeneration, Primary Adrenal Insufficiency, Primary Agammaglobulinemias, Primary Aldosteronism, Primary Alveolar Hypoventilation, Primary Amyloidosis, Primary Anemia, Primary Anemia, Primary Beriberi, Primary Biliary, Primary Biliary Cirrhosis, Primary Brown Syndrome, Primary Carnitine Deficiency, Primary Central Hypoventilation Syndrome, Primary Ciliary Dyskinesia
- 10 Kartagener Type, Primary Cutaneous Amyloidosis, Primary Dystonia, Primary Failure Adrenocortical Insufficiency, Primary Familial Hypoplasia of the Maxilla, Primary Hemochromatosis, Primary Hyperhidrosis, Primary Hyperoxaluria [Type I], Primary Hyperoxaluria Type I (PH1), Primary Hyperoxaluria Type 1, Primary Hyperoxaluria Type II, Primary Hyperoxaluria Type III, Primary Hypogonadism, Primary Intestinal
- 15 Lymphangiectasia, Primary Lateral Sclerosis, Primary Nonhereditary Amyloidosis, Primary Obliterative Pulmonary Vascular Disease, Primary Progressive Multiple Sclerosis, Primary Pulmonary Hypertension, Primary Reading Disability, Primary Renal Glycosuria, Primary Sclerosing Cholangitis, Primary Thrombocytemia, Primary Thrombocytemia, Primary Tumors of Central Nervous System, Primary Visual Agnosia, Proctocolitis
- 20 Idiopathic, Proctocolitis Idiopathic, Progeria of Adulthood, Progeria of Childhood, Progeroid Nanism, Progeroid Short Stature with Pigmented Nevi, Progeroid Syndrome of De Barys, Progressive Autonomic Failure with Multiple System Atrophy, Progressive Bulbar Palsy, Progressive Bulbar Palsy Included, Progressive Cardiomyopathic Lentiginosis, Progressive Cerebellar Ataxia Familial, Progressive Cerebral Poliodystrophy,
- 25 Progressive Choroidal Atrophy, Progressive Diaphyseal Dysplasia, Progressive Diaphyseal Dysplasia, Progressive Facial Hemiatrophy, Progressive Familial Myoclonic Epilepsy, Progressive Hemifacial Atrophy, Progressive Hypothyroidism, Progressive Infantile Poliodystrophy, Progressive Lenticular Degeneration, Progressive Lipodystrophy, Progressive Muscular Dystrophy of Childhood, Progressive Myoclonic Epilepsy,
- 30 Progressive Osseous Heteroplasia, Progressive Pallid Degeneration Syndrome, Progressive Pallid Degeneration Syndrome, Progressive Spinobulbar Muscular Atrophy, Progressive

- Supranuclear Palsy, Progressive Systemic Sclerosis, Progressive Tapetochoroidal Dystrophy, Proline Oxidase Deficiency, Propionic Acidemia, Propionic Acidemia, Propionic Acidemia Type I (PCCA Deficiency), Propionic Acidemia Type II (PCCB Deficiency), Propionyl CoA Carboxylase Deficiency, Propionyl CoA Carboxylase Deficiency, Protanomaly, Protanopia, Protein-Losing Enteropathy Secondary to Congestive Heart Failure, Proteus Syndrome, Proximal Deletion of 4q Included, Proximal Deletion of 4q-Included, PRP, PRS, Prune Belly Syndrome, PS, Pseudo-Hurler Polydystrophy, Pseudo-Polydystrophy, Pseudoacanthosis Nigricans, Pseudoachondroplasia, Pseudocholinesterase Deficiency, Pseudogout Familial, Pseudohemophilia, Pseudohermaphroditism, Pseudohermaphroditism, Pseudohermaphroditism-Nephron Disorder-Wilm's Tumor, Pseudohypertrophic Muscular Dystrophy, Pseudohypoparathyroidism, Pseudohypoparathyroidism, Pseudohypophosphatasia, Pseudopolydystrophy, Pseudothalidomide Syndrome, Pseudoxanthoma Elasticum, Pseudoxanthoma Elasticum, Psoriasis, Psorospermosis Follicularis, PSP, PSS, Psychomotor Convulsion, Psychomotor Epilepsy, Psychomotor Equivalent Epilepsy, PTC Deficiency, Pterygium, Pterygium Colli Syndrome, Pterygium Universale, Pterygolymphangiectasia, Pulmonary Atresia, Pulmonary Lymphangiomyomatosis, Pulmonary Stenosis, Pulmonic Stenosis-Ventricular Septal Defect, Pulp Stones, Pulpal Dysplasia, Pulseless Disease, Pure Alymphocytosis, Pure Cutaneous Histiocytosis, Purine Nucleoside Phosphorylase Deficiency, Purpura Hemorrhagica, Purtilo Syndrome, PXE, PXE Dominant Type, PXE Recessive Type, Pycnodynóstosis, Pyknodynóstosis, Pyknoepilepsy, Pyroglutamic Aciduria, Pyroglutamicaciduria, Pyrroline Carboxylate Dehydrogenase Deficiency, Pyruvate Carboxylase Deficiency, Pyruvate Carboxylase Deficiency Group A, Pyruvate Carboxylase Deficiency Group B, Pyruvate Dehydrogenase Deficiency, Pyruvate Dehydrogenase Deficiency, Pyruvate Dehydrogenase Deficiency, Pyruvate Kinase Deficiency, q25-qter, q26 or q27-qter, q31 or 32-qter, QT Prolongation with Extracellular Hypohypocalcemia, QT Prolongation without Congenital Deafness, QT Prolonged with Congenital Deafness, Quadriplegia of Cerebral Palsy, Quadriplegia of Cerebral Palsy, Quantal Squander, Quantal Squander, r4, r6, r14, r18, r21, r22, Rachischisis Posterior, Radial Aplasia-Amegakaryocytic Thrombocytopenia, Radial Aplasia-Thrombocytopenia

- Syndrome, Radial Nerve Palsy, Radicular Neuropathy Sensory, Radicular Neuropathy Sensory, Radicular Neuropathy Sensory Recessive, Radicular Dentin Dysplasia, Rapid-onset Dystonia-parkinsonism, Rapp-Hodgkin Syndrome, Rapp-Hodgkin (hypohidrotic). Ectodermal Dysplasia syndrome, Rapp-Hodgkin Hypohidrotic Ectodermal Dysplasias,
- 5 Rare hereditary ataxia with polyneuritic changes and deafness caused by a defect in the enzyme phytanic acid hydroxylase, Rautenstrauch-Wiedemann Syndrome, Rautenstrauch-Wiedemann Type Neonatal Progeria, Raynaud's Phenomenon, RDP, Reactive Functional Hypoglycemia, Reactive Hypoglycemia Secondary to Mild Diabetes, Recessive Type Kenny-Caffe Syndrome, Recklin Recessive Type Myotonia Congenita, Recklinghausen Disease, Rectoperineal Fistula, Recurrent Vomiting, Reflex Neurovascular Dystrophy, Reflex Sympathetic Dystrophy Syndrome, Refractive Errors, Refractory Anemia, Refrigeration Palsy, Refsum Disease, Refsum's Disease, Regional Enteritis, Reid-Barlow's syndrome, Reifenstein Syndrome, Reifenstein Syndrome, Reiger Anomaly-Growth Retardation, Reiger Syndrome, Reimann Periodic Disease, Reimann's Syndrome, Reis-
- 10 Bucklers Corneal Dystrophy, Reiter's Syndrome, Reiter's Syndrome, Relapsing Guillain-Barre Syndrome, Relapsing-Remitting Multiple Sclerosis, Renal Agenesis, Renal Dysplasia-Blindness Hereditary, Renal Dysplasia-Retinal Aplasia Loken-Senior Type, Renal Glycosuria, Renal Glycosuria Type A, Renal Glycosuria Type B, Renal Glycosuria Type O, Renal-Oculocerebrodystrophy, Renal-Retinal Dysplasia with Medullary Cystic
- 15 Disease, Renal-Retinal Dysplasia with Medullary Cystic Disease, Renal-Retinal Dystrophy Familial, Renal-Retinal Syndrome, Rendu-Osler-Weber Syndrome, Respiratory Acidosis, Respiratory Chain Disorders, Respiratory Myoclonus, Restless Legs Syndrome, Restrictive Cardio myopathy, Retention Hyperlipemia, Rethore Syndrome (obsolete), Reticular Dysgenesis, Retinal Aplastic-Cystic Kidneys-Joubert Syndrome, Retinal Cone
- 20 Degeneration, Retinal Cone Dystrophy, Retinal Cone-Rod Dystrophy, Retinitis Pigmentosa, Retinitis Pigmentosa and Congenital Deafness, Retinoblastoma, Retinol Deficiency, Retinoschisis, Retinoschisis Juvenile, Retraction Syndrome, Retrobulbar Neuropathy, Retrolenticular Syndrome, Rett Syndrome, Reverse Coarction, Reye Syndrome; Reye's Syndrome, RGS, Rh Blood Factors, Rh Disease, Rh Factor
- 25 Incompatibility, Rh Incompatibility, Rhesus Incompatibility, Rheumatic Fever, Rheumatoid Arthritis, Rheumatoid Myositis, Rhinosinusogenic Cerebral Arachnoiditis,

- Rhizomelic Chondrodysplasia Punctata (RCDP), Acatalasemia, Classical Refsum disease, RHS, Rhythmic Myoclonus, Rib Gap Defects with Micrognathia, Ribbing Disease (obsolete), Ribbing Disease, Richner-Hanhart Syndrome, Rieger Syndrome, Rieter's Syndrome, Right Ventricular Fibrosis, Riley-Day Syndrome, Riley-Smith syndrome, Ring
- 5 Chromosome 14, Ring Chromosome 18, Ring 4, Ring 4 Chromosome, Ring 6, Ring 6 Chromosome, Ring 9, Ring 9 Chromosome R9, Ring 14, Ring 15, Ring 15 Chromosome (mosaic pattern), Ring 18, Ring Chromosome 18, Ring 21, Ring 21 Chromosome, Ring 22, Ring 22 Chromosome, Ritter Disease, Ritter-Lyell Syndrome, RLS, RMSS, Roberts SC- Phocomelia Syndrome, Roberts Syndrome, Roberts Tetraphocomelia Syndrome,
- 10 Robertson's Ectodermal Dysplasias, Robin Anomaly, Robin Sequence, Robin Syndrome, Robinow Dwarfism, Robinow Syndrome, Robinow Syndrome Dominant Form, Robinow Syndrome Recessive Form, Rod myopathy, Roger Disease, Rokitansky's Disease, Romano-Ward Syndrome, Romberg Syndrome, Rootless Teeth, Rosenberg-Chitorian Syndrome, Rosewater Syndrome, Rosewater Syndrome, Rosselli-Gulienatti Syndrome,
- 15 Rothmund-Thomson Syndrome, Roux-Levy Syndrome, RP, RS X-Linked, RS, RS, RSDS, RSH Syndrome, RSS, RSTS, RTS, RTS, Rubella Congenital, Rubinstein Syndrome, Rubinstein-Taybi Syndrome, Rubinstein Taybi Broad Thumb-Hallux syndrome, Rufous Albinism, Ruhr's Syndrome, Russell's Diencephalic Cachexia, Russell's Syndrome, Russell Syndrome, Russell-Silver Dwarfism, Russell-Silver Syndrome, Russell-Silver Syndrome X-linked, Ruvalcaba-Myhre-Smith syndrome (RMSS), Ruvalcaba Syndrome, Ruvalcaba Type Osseous Dysplasia with Mental Retardation, Sacral Regression, Sacral Agenesis Congenital, SAE, Saethre-Chotzen Syndrome, Sakati, Sakati Syndrome, Sakati-Nyhan Syndrome, Salaam Spasms, Salivosudoriparous Syndrome, Salzman Nodular Corneal Dystrophy, Sandhoff Disease,
- 20 Sanfilippo Syndrome, Sanfilippo Type A, Sanfilippo Type B, Santavuori Disease, Santavuori-Haltia Disease, Sarcoid of Boeck, Sarcoidosis, Sarcoidosis, Sathre-chotzen, Saturday Night Palsy, SBMA, SC Phocomelia Syndrome, SC Syndrome, SCA 3, SCAD Deficiency, SCAD Deficiency Adult-Onset Localized, SCAD Deficiency Congenital Generalized, SCAD, SCAD, SCAD, SCADH Deficiency, Scalded Skin Syndrome, Scalp
- 25 Defect Congenital, Scaphocephaly, Scaphocephaly, Scaphocephaly, Scapula Elevata, Scapuloperoneal myopathy, Scapuloperoneal Muscular Dystrophy, Scapuloperoneal

Syndrome Myopathic Type, Scarring Bullosa, Scarring Bullosa, SCHAD, Schaumann's Disease, Scheie Syndrome, Schereshevskii-Turner Syndrome, Schilder Disease, Schilder Encephalitis, Schilder's Disease, Schindler Disease Type I (Infantile Onset), Schindler Disease Infantile Onset, Schindler Disease, Schindler Disease Type II (Adult Onset),  
5 Schinzel Syndrome, Schinzel-Giedion Syndrome, Schinzel Acrocallosal Syndrome, Schinzel-Giedion Midface-Retraction Syndrome, Schizencephaly, Schmid Type Metaphyseal Chondrodysplasia, Schmid Metaphyseal Dysostosis, Schmid-Fraccaro Syndrome, Schmidt Syndrome, Schopf-Schultz-Passarge Syndrome, Schueller-Christian Disease, Schut-Haymaker Type, Schwartz-Jampel-Aberfeld Syndrome, Schwartz-Jampel  
10 Syndrome Types 1A and 1B, Schwartz-Jampel Syndrome, Schwartz-Jampel Syndrome Type 2, SCI, D SCID, Scleroderma, Scleroderma, Sclerosis Familial Progressive Systemic, Sclerosis Diffuse Familial Brain, Scott Craniodigital Syndrome With Mental Retardation, Scrotal Tongue, SCS, SCS, SD, SDS, SDYS, Seasonal Conjunctivitis, Sebaceous Nevus Syndrome, Sebaceous nevus, Seborrheic Keratosis, Seborrheic Warts, Seckel Syndrome,  
15 Seckel Type Dwarfism, Second Degree Congenital Heart Block, Secondary Amyloidosis, Secondary Blepharospasm, Secondary Non-tropical Sprue, Secondary Brown Syndrome, Secondary Beriberi, Secondary Generalized Amyloidosis, Secondary Dystonia, Secretory Component Deficiency, Secretory IgA Deficiency, SED Tarda, SED Congenital, SEDC, Segmental linear achromic nevus, Segmental Dystonia, Segmental Myoclonus, Seip  
20 Syndrome, Seitelberger Disease, Seitelberger Disease, Seizures, Selective Deficiency of IgG Subclasses, Selective Mutism, Selective Deficiency of IgG Subclass, Selective IgM Deficiency, Selective Mutism, Selective IgA Deficiency, Self-Healing Histiocytosis, Semilobar Holoprosencephaly, Seminiferous Tubule Dysgenesis, Senile Retinoschisis, Senile Warts, Senior-Loken Syndrome, Sensory Neuropathy Hereditary Type I, Sensory  
25 Neuropathy Hereditary Type II, Sensory Neuropathy Hereditary Type I, Sensory Radicular Neuropathy, Sensory Radicular Neuropathy, Sensory Radicular Neuropathy Recessive, Septic Progressive Granulomatosis, Septo-Optic Dysplasia, Serous Circumscribed Meningitis, Serum Protease Inhibitor Deficiency, Serum Carnosinase Deficiency, Setleis Syndrome, Severe Combined Immunodeficiency, Severe Combined Immunodeficiency  
30 with Adenosine Deaminase Deficiency, Severe Combined Immunodeficiency (SCID), Sex Reversal, Sexual Infantilism, SGB Syndrome, Sheehan Syndrome, Shields Type

- Dentinogenesis Imperfecta, Shingles, varicella-zoster virus, Ship Beriberi, SHORT Syndrome, Short Arm 18 Deletion Syndrome, Short Chain Acyl CoA Dehydrogenase Deficiency, Short Chain Acyl-CoA Dehydrogenase (SCAD) Deficiency, Short Stature and Facial Telangiectasis, Short Stature Facial/Skeletal Anomalies-Retardation-Macrodontia,
- 5 Short Stature-Hyperextensibility-Rieger Anomaly-Teething Delay, Short Stature-Onychodysplasia, Short Stature Telangiectatic Erythema of the Face, SHORT Syndrome, Shoshin Beriberi, Shoulder girdle syndrome, Shprintzen-Goldberg Syndrome, Shulman Syndrome, Shwachman-Bodian Syndrome, Shwachman-Diamond Syndrome, Shwachman Syndrome, Shwachman-Diamond-Oski Syndrome, Shwachmann Syndrome, Shy Drager Syndrome, Shy-Magee Syndrome, SI Deficiency, Sialidase Deficiency, Sialidosis Type I Juvenile, Sialidosis Type II Infantile, Sialidosis, Sialolipidosis, Sick Sinus Syndrome, Sickle Cell Anemia, Sickle Cell Disease, Sickle Cell-Hemoglobin C Disease, Sickle Cell-Hemoglobin D Disease, Sickle Cell-Thalassemia Disease, Sickle Cell Trait, Sideroblastic Anemias, Sideroblastic Anemia, Sideroblastosis, Sideroblastosis, SIDS, Siegel-Cattan-
- 10 Mamou Syndrome, Siemens-Bloch type Pigmented Dermatoses, Siemens Syndrome, Siewerling-Creutzfeldt Disease, Siewert Syndrome, Silver Syndrome, Silver-Russell Dwarfism, Silver-Russell Syndrome, Simmond's Disease, Simons Syndrome, Simplex Epidermolysis Bullosa, Simpson Dysmorphia Syndrome, Simpson-Golabi-Behmel Syndrome, Sinding-Larsen-Johansson Disease, Singleton-Merten Syndrome, Sinus
- 15 Arrhythmia, Sinus Venosus, Sinus tachycardia, Sirenomelia Sequence, Sirenomelus, Situs Inversus Bronchiectasis and Sinusitis, SJA Syndrome, Sjogren Larsson Syndrome Ichthyosis, Sjogren Syndrome, Sjogren Larsson Syndrome Ichthyosis, Sjögren's Syndrome, SJS, Skeletal dysplasia, Skeletal Dysplasia Weismann Netter Stuhl Type, Skin Peeling Syndrome, Skin Neoplasms, Skull Asymmetry and Mild Retardation, Skull
- 20 Asymmetry and Mild Syndactyly, SLE, Sleep Epilepsy, Sleep Apnea, SLO, Sly Syndrome, SMA, SMA Infantile Acute Form, SMA I, SMA III, SMA type I, SMA type II, SMA type III, SMA3, SMAX1, SMCR, Smith Lemli Opitz Syndrome, Smith Magenis Syndrome, Smith-Magenis Chromosome Region, Smith-McCort Dwarfism, Smith-Opitz-Inborn Syndrome, Smith Disease, Smoldering Myeloma, SMS, SMS, SNE, Sneezing From Light
- 25 Exposure, Sodium valproate, Solitary Plasmacytoma of Bone, Sorsby Disease, Sotos Syndrome, Souques-Charcot Syndrome, South African Genetic Porphyria, Spasmodic
- 30

- Dysphonia, Spasmodic Torticollis, Spasmodic Torticollis, Spasmodic Wryneck, Spastic Cerebral Palsy, Spastic Colon, Spastic Dysphonia, Spastic Paraplegia, SPD Calcinosi, Specific Antibody Deficiency with Normal Immunoglobulins, Specific Reading Disability, SPH2, Spherocytic Anemia, Spherocytosis, Spherophakia-Brachymorphia Syndrome,
- 5 Sphingomyelin Lipidosis, Sphingomyelinase Deficiency, Spider fingers, Spielmeyer-Vogt Disease, Spielmeyer-Vogt-Batten Syndrome, Spina Bifida, Spina Bifida, Spina Bifida Aperta, Spinal Arachnoiditis, Spinal Arteriovenous Malformation, Spinal Ataxia Hereditofamilial, Spinal and Bulbar Muscular Atrophy, Spinal Diffuse Idiopathic Skeletal Hyperostosis, Spinal DISH, Spinal Muscular Atrophy, Spinal Muscular Atrophy, Spinal
- 10 Muscular Atrophy All Types, Spinal Muscular Atrophy Type ALS, Spinal Muscular Atrophy-Hypertrophy of the Calves, Spinal Muscular Atrophy Type I, Spinal Muscular Atrophy Type III, Spinal Muscular Atrophy type 3, Spinal Muscular Atrophy-Hypertrophy of the Calves, Spinal Ossifying Arachnoiditis, Spinal Stenosis, Spino Cerebellar Ataxia, Spinocerebellar Atrophy Type I, Spinocerebellar Ataxia Type I (SCA1), Spinocerebellar
- 15 Ataxia Type II (SCAII), Spinocerebellar Ataxia Type III (SCAIII), Spinocerebellar Ataxia Type III (SCA 3), Spinocerebellar Ataxia Type IV (SCAIV), Spinocerebellar Ataxia Type V (SCAV), Spinocerebellar Ataxia Type VI (SCAVI), Spinocerebellar Ataxia Type VII (SCAVII), Spirochetal Jaundice, Splenic Agenesis Syndrome, Splenic Ptosis, Splenoptosis, Split Hand Deformity-Mandibulofacial Dysostosis, Split Hand Deformity-Mandibulofacial
- 20 Dysostosis, Split Hand Deformity, Split-Hand Deformity, Spondyloarthritis, Spondylocostal Dysplasia - Type I, Spondyloepiphyseal Dysplasia Tarda, Spondylothoracic Dysplasia, Spondylotic Caudal Radiculopathy, Sponge Kidney, Spongioblastoma Multiforme, Spontaneous Hypoglycemia, Sprengel Deformity, Spring Ophthalmia, SRS, ST, Stale Fish Syndrome, Staphyloccal Scalded Skin Syndrome,
- 25 Stargardt's Disease, Startle Disease, Status Epilepticus, Steele-Richardson-Olszewski Syndrome, Steely Hair Disease, Stein-Leventhal Syndrome, Steinert Disease, Stengel's Syndrome, Stengel-Batten-Mayou-Spielmeyer-Vogt-Stock Disease, Stenosing Cholangitis, Stenosis of the Lumbar Vertebral Canal, Stenosis, Steroid Sulfatase Deficiency, Stevanovic's Ectodermal Dysplasias, Stevens Johnson Syndrome, Stevens-Johnson
- 30 Syndrome, STGD, Stickler Syndrome, Stickler Syndrome, Stiff-Man Syndrome, Stiff Man Syndrome, Stiff Person Syndrome, Still's Disease, Stilling-Turk-Duane Syndrome, Stillis

- Disease, Stimulus-Sensitive Myoclonus, Stone Man Syndrome, Stone Man, Streeter Anomaly, Striatonigral Degeneration Autosomal Dominant Type, Striopallidodentate Calcinosis, Stroma, Descemet's Membrane, Stromal Corneal Dystrophy, Struma Lymphomatosa, Sturge-Kalischer-Weber Syndrome, Sturge Weber Syndrome, Sturge-  
5 Weber Phakomatosis, Subacute Necrotizing Encephalomyelopathy, Subacute Necrotizing Encephalomyelopathy, Subacute Spongiform Encephalopathy, Subacute Necrotizing Encephalopathy, Subacute Sarcoidosis, Subacute Neuronopathic, Subaortic Stenosis, Subcortical Arteriosclerotic Encephalopathy, Subendocardial Sclerosis, Succinylcholine Sensitivity, Sucrase-Isomaltase Deficiency Congenital, Sucrose-Isomaltose Malabsorption  
10 Congenital, Sucrose Intolerance Congenital, Sudanophilic Leukodystrophy ADL, Sudanophilic Leukodystrophy Pelizaeus-Merzbacher Type, Sudanophilic Leukodystrophy Included, Sudden Infant Death Syndrome, Sudeck's Atrophy, Sugio-Kajii Syndrome, Summerskill Syndrome, Summit Acrocephalosyndactyly, Summitt's Acrocephalosyndactyly, Summitt Syndrome, Superior Oblique Tendon Sheath Syndrome,  
15 Suprarenal glands, Supravalvular Aortic Stenosis, Supraventricular tachycardia, Surdicardiac Syndrome, Surdocardiac Syndrome, SVT, Sweat Gland Abscess, Sweating Gustatory Syndrome, Sweet Syndrome, Swiss Cheese Cartilage Syndrome, Syndactylic Oxycephaly, Syndactyly Type I with Microcephaly and Mental Retardation, Syndromatic Hepatic Ductular Hypoplasia, Syringomyelia, Systemic Aleukemic Reticuloendotheliosis,  
20 Systemic Amyloidosis, Systemic Carnitine Deficiency, Systemic Elastorrhexis, Systemic Lupus Erythematosus, Systemic Mast Cell Disease, Systemic Mastocytosis, Systemic-Onset Juvenile Arthritis, Systemic-Onset Juvenile Arthritis, Systemic Sclerosis, Systopic Spleen, T-Lymphocyte Deficiency, Tachyalimentation Hypoglycemia, Tachycardia, Takahara syndrome, Takayasu Disease, Takayasu Arteritis, Takayasu Arteritis, Talipes  
25 Calcaneus, Talipes Equinovarus, Talipes Equinus, Talipes Varus, Talipes Valgus, Tandem Spinal Stenosis, Tangier Disease, Tapetoretinal Degeneration, TAR Syndrome, Tardive Dystonia, Tardive Muscular Dystrophy, Tardive Dyskinesia, Tardive Oral Dyskinesia, Tardive Dyskinesia, Tardive Dystonia, Tardy Ulnar Palsy, Target Cell Anemia, Tarsomegaly, Tarui Disease, TAS Midline Defects Included, TAS Midline Defect, Tay  
30 Sachs Disease, Tay Sachs Sphingolipidosis, Tay Sachs Disease, Tay Syndrome Ichthyosis, Tay Sachs Sphingolipidosis, Tay Syndrome Ichthyosis, Taybi Syndrome Type I, Taybi

- Syndrome, TCD, TCOF1, TCS, TD, TDO Syndrome, TDO-I, TDO-II, TDO-III, Telangiectasis, Telecanthus with Associated Abnormalities, Telecanthus With Associated Abnormalities, Telecanthus-Hypospadias Syndrome, Temporal Lobe Epilepsy, Temporal Arteritis/Giant Cell Arteritis, Temporal Arteritis, TEN, Tendon Sheath Adherence Superior
- 5 Obliquus, Tension Myalgia, Terminal Deletion of 4q Included, Terminal Deletion of 4q-Included, Terrian Corneal Dystrophy, Teschler-Nicola/Killian Syndrome, Tethered Spinal Cord Syndrome, Tethered Cord Malformation Sequence, Tethered Cord Syndrome, Tethered Cervical Spinal Cord Syndrome, Tetrahydrobiopterin Deficiencies, Tetrahydrobiopterin Deficiencies, Tetralogy of Fallot, Tetralogy of Fallot,
- 10 Tetraphocomelia-Thrombocytopenia Syndrome, Tetrasomy Short Arm of Chromosome 9, Tetrasomy 9p, Tetrasomy Short Arm of Chromosome 18, Thalamic Syndrome, Thalamic Pain Syndrome, Thalamic Hyperesthetic Anesthesia, Thalassemia Intermedia, Thalassemia Minor, Thalassemia Major, Thiamine Deficiency, Thiamine-Responsive Maple Syrup Urine Disease, Thin-Basement-Membrane Nephropathy, Thiolase deficiency, RCDP, Acyl-
- 15 CoA dihydroxyacetonephosphate acyltransferase, Third and Fourth Pharyngeal Pouch Syndrome, Third Degree Congenital (Complete) Heart Block, Thomsen Disease, Thoracic-Pelvic-Phalangeal Dystrophy, Thoracic Spinal Canal, Thoracoabdominal Syndrome, Thoracoabdominal Ectopia Cordis Syndrome, Three M Syndrome, Three-M Slender-Boned Nanism, Thrombasthenia of Glanzmann and Naegeli, Thrombocythemia Essential,
- 20 Thrombocytopenia-Absent Radius Syndrome, Thrombocytopenia-Hemangioma Syndrome, Thrombocytopenia-Absent Radii Syndrome, Thrombophilia Hereditary Due to AT III, Thrombotic Thrombocytopenic Purpura, Thromboulcerative Colitis, Thromboulcerative Colitis, Thymic Dysplasia with Normal Immunoglobulins, Thymic Agenesis, Thymic Aplasia DiGeorge Type, Thymic Hypoplasia Agammaglobulinemias
- 25 Primary Included, Thymic Hypoplasia DiGeorge Type, Thymus Congenital Aplasia, Tic Douloureux, Tics, Tinel's syndrome, Tolosa Hunt Syndrome, Tonic Spasmodic Torticollis, Tonic Pupil Syndrome, Tooth and Nail Syndrome, Tooth and Nail Syndrome, Torch Infection, TORCH Syndrome, Torsion Dystonia, Torticollis, Torticollis, Total Lipodystrophy, Total anomalous pulmonary venous connection, Touraine's Aphthosis,
- 30 Tourette Syndrome, Tourette's disorder, Townes-Brocks Syndrome, Townes Syndrome, Toxic Paralytic Anemia, Toxic Epidermal Necrolysis, Toxopachyosteose Diaphysaire

Tibio-Peroniere, Toxopachyosteose, Toxoplasmosis Other Agents Rubella  
Cytomegalovirus Herpes Simplex, Tracheoesophageal Fistula with or without Esophageal  
Atresia, Tracheoesophageal Fistula, Transient neonatal myasthenia gravis, Transitional  
Atrioventricular Septal Defect, Transposition of the great arteries, Transtelephonic  
5 Monitoring, Transthyretin Methionine-30 Amyloidosis (Type I), Trapezoidocephaly-  
Multiple Synostosis Syndrome, Treacher Collins Syndrome, Treacher Collins-  
Franceschetti Syndrome 1, Trevor Disease, Triatrial Heart, Tricho-Dento-Osseous  
Syndrome, Trichodento Osseous Syndrome, Trichopoliodystrophy, Trichorhinophalangeal  
Syndrome, Trichorhinophalangeal Syndrome, Tricuspid atresia, Trifunctional Protein  
10 Deficiency, Trigeminal Neuralgia, Triglyceride Storage Disease Impaired Long-Chain  
Fatty Acid Oxidation, Trigonitis, Trigonocephaly, Trigonocephaly, Trigonocephaly,  
Trigonocephaly Syndrome, Trigonocephaly "C" Syndrome, Trimethylaminuria,  
Triphalangeal Thumbs-Hypoplastic Distal Phalanges-Onychodystrophy, Triphalangeal  
Thumb Syndrome, Triple Symptom Complex of Behcet, Triple X Syndrome, Triplo X  
15 Syndrome, Triploid Syndrome, Triploidy, Triploidy Syndrome, Trismus-  
Pseudocamptodactyly Syndrome, Trisomy, Trisomy G Syndrome, Trisomy X, Trisomy 6q  
Partial, Trisomy 6q Syndrome Partial, Trisomy 9 Mosaic, Trisomy 9P Syndrome (Partial)  
Included, Trisomy 11q Partial, Trisomy 14 Mosaic, Trisomy 14 Mosaicism Syndrome,  
Trisomy 21 Syndrome, Trisomy 22 Mosaic, Trisomy 22 Mosaicism Syndrome, TRPS,  
20 TRPS1, TRPS2, TRPS3, True Hermaphroditism, True Hermaphroditism, Truncus  
arteriosus, Tryptophan Malabsorption, Tryptophan Pyrrolase Deficiency, TS, TTP, TTTS,  
Tuberous Sclerosis, Tubular Ectasia, Turcot Syndrome, Turner Syndrome, Turner-Kieser  
Syndrome, Turner Phenotype with Normal Chromosomes (Karyotype), Turner-Varny  
Syndrome, Turricephaly, Twin-Twin Transfusion Syndrome, Twin-to-Twin Transfusion  
25 Syndrome, Type A, Type B, Type AB, Type O, Type I Diabetes, Type I Familial  
Incomplete Male, Type I Familial Incomplete Male Pseudohermaphroditism, Type I  
Gaucher Disease, Type I (PCCA Deficiency), Type I Tyrosinemia, Type II Gaucher  
Disease, Type II Histiocytosis, Type II (PCCB Deficiency), Type II Tyrosinemia, Type  
IIA Distal Arthrogryposis Multiplex Congenita, Type III Gaucher Disease, Type III  
30 Tyrosinemia, Type III Dentinogenesis Imperfecta, Typical Retinoschisis, Tyrosinase  
Negative Albinism (Type I), Tyrosinase Positive Albinism (Type II), Tyrosinemia type 1

- acute form, Tyrosinemia type 1 chronic form, Tyrosinosis, UCE, Ulcerative Colitis, Ulcerative Colitis Chronic Non-Specific, Ulnar-Mammary Syndrome, Ulnar-Mammary Syndrome of Pallister, Ulnar Nerve Palsy, UMS, Unclassified FODs, Unconjugated Benign Bilirubinemav, Underactivity of Parathyroid, Unilateral Ichthyosiform
- 5 Erythroderma with Ipsilateral Malformations Limb, Unilateral Chondromatosis, Unilateral Defect of Pectoralis Muscle and Syndactyly of the Hand, Unilateral Hemidysplasia Type, Unilateral Megalencephaly, Unilateral Partial Lipodystrophy, Unilateral Renal Agenesis, Unstable Colon, Unverricht Disease, Unverricht-Lundborg Disease, Unverricht-Lundborg-Laf Disease, Unverricht Syndrome, Upper Limb - Cardiovascular Syndrome (Holt-Oram),
- 10 Upper Motor Neuron Disease, Upper Airway Apnea, Upper Airway Apnea, Urea Cycle Defects or Disorders, Urea Cycle Disorder Arginase Type, Urea Cycle Disorder Arginino Succinase Type, Urea Cycle Disorders Carbamyl Phosphate Synthétase Type, Urea Cycle Disorder Citrullinemia Type, Urea Cycle Disorders N-Acetyl Glutamate Synthetase Typ, Urea Cycle Disorder OTC Type, Urethral Syndrome, Urethro-Oculo-Articular Syndrome,
- 15 Uridine Diphosphate Glucuronosyltransferase Severe Def. Type I, Urinary Tract Defects, Urofacial Syndrome, Uroporphyrinogen III cosynthase, Urticaria pigmentosa, Usher Syndrome, Usher Type I, Usher Type II, Usher Type III, Usher Type IV, Uterine Synechia, Uroporphyrinogen I-synthase, Uveitis, Uveomeningitis Syndrome, V-CJD, VACTEL Association, VACTERL Association, VACTERL Syndrome, Valgus Calcaneus,
- 20 Valine Transaminase Deficiency, Valinemia, Valproic Acid, Valproate acid exposure, Valproic acid exposure, Valproic acid, Van Buren's Disease, Van der Hoeve-Habertsma-Waardenburg-Gauldi Syndrome, Variable Onset Immunoglobulin Deficiency Dysgammaglobulinemia, Variant Creutzfeldt-Jakob Disease (V-CJD), Varicella Embryopathy, Variegate Porphyria, Variegate Porphyria, Variegate Porphyria, Vascular
- 25 Birthmarks, Vascular Dementia Binswanger's Type, Vascular Erectile Tumor, Vascular Hemophilia, Vascular Malformations, Vascular Malformations of the Brain, Vasculitis, Vasomotor Ataxia, Vasopressin-Resistant Diabetes Insipidus, Vasopressin-Sensitive Diabetes Insipidus, VATER Association, Vcf syndrome, Vcfs, Velocardiofacial Syndrome, VeloCardioFacial Syndrome, Venereal Arthritis, Venous Malformations, Ventricular
- 30 Fibrillation, Ventricular Septal Defects, Congenital Ventricular Defects, Ventricular Septal Defect, Ventricular Tachycardia, Venual Malformations, VEOHD, Vermis Aplasia,

- Vermis Cerebellar Agenesis, Vernal Keratoconjunctivitis, Verruca, Vertebral Anal Tracheoesophageal Esophageal Radial, Vertebral Ankylosing Hyperostosis, Very Early Onset Huntington's Disease, Very Long Chain Acyl-CoA Dehydrogenase (VLCAD) Deficiency, Vestibular Schwannoma, Vestibular Schwannoma Neurofibromatosis,
- 5 Vestibulocerebellar, Virchow's Oxycephaly, Visceral Xanthogranulomatosis, Visceral Xantho-Granulomatosis, Visceral myopathy-External Ophthalmoplegia, Visceromegaly-Umbilical Hernia-Macroglossia Syndrome, Visual Amnesia, Vitamin A Deficiency, Vitamin B-1 Deficiency, Vitelline Macular Dystrophy, Vitiligo, Vitiligo Capitis, Vitreoretinal Dystrophy, VKC, VKH Syndrome, VLCAD, VLCAD, Vogt Syndrome, Vogt
- 10 Cephalosyndactyly, Vogt Koyanagi Harada Syndrome, Vogt Koyanagi Harada Syndrome, Vogt Koyanagi Harada Syndrome, Von Bechterew-Strumpell Syndrome, Von Eulenburg Paramyotonia Congenita, Von Frey's Syndrome, Von Gierke Disease, Von Hippel-Lindau Syndrome, Von Mikulicz Syndrome, Von Recklinghausen Disease, Von Willebrandt Disease, VP, Vrolik Disease (Type II), VSD, VSD, Vulgaris Type Disorder of
- 15 Cornification, Vulgaris Type Ichthyosis, W Syndrome, Waardenburg Syndrome, Waardenburg-Klein Syndrome, Waardenburg Syndrome Type I (WS1), Waardenburg Syndrome Type II (WS2), Waardenburg Syndrome Type IIA (WS2A), Waardenburg Syndrome Type IIB (WS2B), Waardenburg Syndrome Type III (WS3), Waardenburg Syndrome Type IV (WS4), Waelsch's Syndrome, WAGR Complex, WAGR Syndrome,
- 20 WAGR Syndrome, Waldenstroem's Macroglobulinemia, Waldenstrom's Purpura, Waldenstrom's Syndrome, Waldmann Disease, Walker-Warburg Syndrome, Wandering Spleen, Warburg Syndrome, Warm Antibody Hemolytic Anemia, Warm Reacting Antibody Disease, Wartenberg Syndrome, WAS, Water on the Brain, Watson Syndrome, Watson-Alagille Syndrome, Waterhouse-Friderichsen syndrome, Waxy Disease, WBS,
- 25 Weaver Syndrome, Weaver-Smith Syndrome, Weber-Cockayne Disease, Wegener's Granulomatosis, Wegener's Granulomatosis, Weil Disease, Weil Syndrome, Weill-Marchesani, Weill-Marchesani Syndrome, Weill-Reyes Syndrome, Weismann-Netter-Stuhl Syndrome, Weissenbacher-Zweymuller Syndrome, Wells Syndrome, Wenckebach, Werdnig-Hoffman Disease, Werdnig-Hoffmann Disease, Werdnig-Hoffmann disease,
- 30 Werdnig-Hoffman Disease, Werdnig-Hoffman Paralysis, Werlhof's Disease, Werner Syndrome, Wernicke's (C) I Syndrome, Wernicke's aphasia, Wernicke-Korsakoff

- Syndrome, West Syndrome, Wet Beriberi, WHCR, Whipple's Disease, Whipple Disease, Whistling face syndrome, Whistling Face-Windmill Vane Hand Syndrome, White-Darier Disease, Whitnall-Norman Syndrome, Whorled nevoid hypermelanosis, WHS, Wieacker Syndrome, Wieacker Syndrome, Wieacker-Wolff Syndrome, Wiedemann-Beckwith  
5 Syndrome, Wiedemann-Rautenstrauch Syndrome, Wildervanck Syndrome, Willebrand-Juergens Disease, Willi-Prader Syndrome, Williams Syndrome, Williams Syndrome, Williams-Beuren Syndrome, Wilms' Tumor, Wilms' Tumor-Aniridia-Gonadoblastoma-Mental Retardation Syndrome, Wilms Tumor Aniridia Gonadoblastoma Mental Retardation, Wilms' Tumor-Aniridia-Genitourinary Anomalies-Mental Retardation  
10 Syndrome, Wilms Tumor-Pseudohermaphroditism-Nephropathy, Wilms Tumor and Pseudohermaphroditism, Wilms Tumor-Pseudohermaphroditism-Glomerulopathy, Wilson's Disease, Winchester Syndrome, Winchester-Grossman Syndrome, Wiskott-Aldrich Syndrome, Wiskott-Aldrich Type Immunodeficiency, Witkop Ectodermal Dysplasias, Witkop Tooth-Nail Syndrome, Wittmaack-Ekbom Syndrome, WM Syndrome,  
15 WMS, WMS, WNS, Wohlfart-Disease, Wohlfart-Kugelberg-Welander Disease, Wolf Syndrome, Wolf-Hirschhorn Chromosome Region (WHCR), Wolf-Hirschhorn Syndrome, Wolff-Parkinson-White Syndrome, Wolff-Parkinson-White syndrome, Wolff Parkinson White Syndrome, Wolfram Syndrome, Wolman Disease (Lysosomal Acid Lipase Deficiency), Woody Guthrie's Disease, WPW Syndrome, WPW Syndrome, Writer's  
20 Cramp, WS, WS, WS, WSS, WWS, Wyburn-Mason Syndrome, Wyburn-Mason Syndrome, X-Linked Addison's Disease, X-linked Adrenoleukodystrophy (X-ALD), X-linked Adult Onset Spinobulbar Muscular Atrophy, X-linked Adult Spinal Muscular Atrophy, X-Linked Agammaglobulinemia with Growth Hormone Deficiency, X-Linked Agammaglobulinemia, Lymphoproliferate X-Linked Syndrome, X-linked Cardio  
25 myopathy and Neutropenia, X-Linked Centronuclear myopathy, X-linked Copper Deficiency, X-linked Copper Malabsorption, X-Linked Dominant Conradi-Hunermann Syndrome, X-Linked Dominant Inheritance Agenesis of Corpus Callosum, X-Linked Dystonia-parkinsonism, X-Linked Ichthyosis, X Linked Ichthyosis, X-Linked Infantile Agammaglobulinemia, X-Linked Infantile Necrotizing Encephalopathy, X-linked Juvenile  
30 Retinoschisis, X-linked Lissencephaly, X-linked Lymphoproliferative Syndrome, X-linked Mental Retardation-Clasped Thumb Syndrome, X-Linked Mental Retardation with

- 85 -

- Hypotonia, X-linked Mental Retardation and Macroorchidism, X-Linked Progressive Combined Variable Immunodeficiency, X-Linked Recessive Conradi-Hunermann Syndrome, X-Linked Recessive Severe Combined Immunodeficiency, X-Linked Recessive Severe Combined Immunodeficiency, X-Linked Retinoschisis, X-linked
- 5 Spondyloepiphyseal Dysplasia, Xanthine Oxidase Deficiency (Xanthinuria Deficiency, Hereditary), Xanthinuria Deficiency, Hereditary (Xanthine Oxidase Deficiency), Xanthogranulomatosis Generalized, Xanthoma Tuberous, Xeroderma Pigmentosum, Xeroderma Pigmentosum Dominant Type, Xeroderma Pigmentosum Type A I XPA Classical Form, Xeroderma Pigmentosum Type B II XPB, Xeroderma Pigmentosum Type
- 10 E V XPE, Xeroderma Pigmentosum Type C III XPC, Xeroderma Pigmentosum Type D IV XPD, Xeroderma Pigmentosum Type F VI XPF, Xeroderma Pigmentosum Type G VII XPG, Xeroderma Pigmentosum Variant Type XP-V, Xeroderma-Talipes-and Enamel Defect, Xerodermic Idiocy, Xerophthalmia, Xerotic Keratitis, XLP, XO Syndrome, XP, XX Male Syndrome, Sex Reversal, XXXXX Syndrome, XXY Syndrome, XYY Syndrome,
- 15 XYY Chromosome Pattern, Yellow Mutant Albinism, Yellow Nail Syndrome, YKL, Young Female Arteritis, Yunis-Varon Syndrome, YY Syndrome, Z-E Syndrome, Z- and - Protease Inhibitor Deficiency, Zellweger Syndrome, Zellweger syndrome, Zellweger cerebro-hepato-renal syndrome, ZES, Ziehen-Oppenheim Disease (Torsion Dystonia), Zimmermann-Laband Syndrome, Zinc Deficiency Congenital, Zinsser-Cole-Engman
- 20 Syndrome, ZLS, Zollinger-Ellison Syndrome.

- As used herein a "cancer" refers to a group of diseases and disorders that are characterized by uncontrolled cellular growth (e.g. formation of tumor) without any differentiation of those cells into specialized and different cells. Cancers which can be treated using the
- 25 methods of the present invention include, without being limited to, ABL1 protooncogene, AIDS Related Cancers, Acoustic Neuroma, Acute Lymphocytic Leukaemia, Acute Myeloid Leukaemia, Adenocystic carcinoma, Adrenocortical Cancer, Agnogenic myeloid metaplasia, Alopecia, Alveolar soft-part sarcoma, Anal cancer, Angiosarcoma, Aplastic Anaemia, Astrocytoma, Ataxia-telangiectasia, Basal Cell Carcinoma (Skin), Bladder
- 30 Cancer, Bone Cancers, Bowel cancer, Brain Stem Glioma, Brain and CNS Tumors, Breast Cancer, CNS tumors, Carcinoid Tumors, Cervical Cancer, Childhood Brain Tumors,

- Childhood Cancer, Childhood Leukaemia, Childhood Soft Tissue Sarcoma, Chondrosarcoma, Choriocarcinoma, Chronic Lymphocytic Leukaemia, Chronic Myeloid Leukaemia, Colorectal Cancers, Cutaneous T-Cell Lymphoma, Dermatofibrosarcoma-  
protuberans, Desmoplastic-Small-Round-Cell-Tumor, Ductal Carcinoma, Endocrine  
5 Cancers, Endometrial Cancer, Ependymoma, Esophageal Cancer, Ewing's Sarcoma, Extra-  
Hepatic Bile Duct Cancer, Eye Cancer, Eye: Melanoma, Retinoblastoma, Fallopian Tube  
cancer, Fanconi Anaemia, Fibrosarcoma, Gall Bladder Cancer, Gastric Cancer,  
Gastrointestinal Cancers, Gastrointestinal-Carcinoid-Tumor, Genitourinary Cancers, Germ  
Cell Tumors, Gestational-Trophoblastic-Disease, Glioma, Gynaecological Cancers,  
10 Haematological Malignancies, Hairy Cell Leukaemia, Head and Neck Cancer,  
Hepatocellular Cancer, Hereditary Breast Cancer, Histiocytosis, Hodgkin's Disease,  
Human Papillomavirus, Hydatidiform mole, Hypercalcemia, Hypopharynx Cancer,  
IntraOcular Melanoma, Islet cell cancer, Kaposi's sarcoma, Kidney Cancer, Langerhan's-  
Cell-Histiocytosis, Laryngeal Cancer, Leiomyosarcoma, Leukaemia, Li-Fraumeni  
15 Syndrome, Lip Cancer, Liposarcoma, Liver Cancer, Lung Cancer, Lymphedema,  
Lymphoma, Hodgkin's Lymphoma, Non-Hodgkin's Lymphoma, Male Breast Cancer,  
Malignant-Rhabdoid-Tumor-of-Kidney, Medulloblastoma, Melanoma, Merkel Cell  
Cancer, Mesothelioma, Metastatic Cancer, Mouth Cancer, Multiple Endocrine Neoplasia,  
Mycosis Fungoides, Myelodysplastic Syndromes, Myeloma, Myeloproliferative Disorders,  
20 Nasal Cancer, Nasopharyngeal Cancer, Nephroblastoma, Neuroblastoma,  
Neurofibromatosis, Nijmegen Breakage Syndrome, Non-Melanoma Skin Cancer, Non-  
Small-Cell-Lung-Cancer-(NSCLC), Ocular Cancers, Oesophageal Cancer, Oral cavity  
Cancer, Oropharynx Cancer, Osteosarcoma, Ostomy Ovarian Cancer, Pancreas Cancer,  
Paranasal Cancer, Parathyroid Cancer, Parotid Gland Cancer, Penile Cancer, Peripheral-  
25 Neuroectodermal-Tumors, Pituitary Cancer, Polycythemia vera, Prostate Cancer, Rare-  
cancers-and-associated-disorders, Renal Cell Carcinoma, Retinoblastoma,  
Rhabdomyosarcoma, Rothmund-Thomson Syndrome, Salivary Gland Cancer, Sarcoma,  
Schwannoma, Sezary syndrome, Skin Cancer, Small Cell Lung Cancer (SCLC), Small  
Intestine Cancer, Soft Tissue Sarcoma, Spinal Cord Tumors, Squamous-Cell-Carcinoma-  
30 (skin), Stomach Cancer, Synovial sarcoma, Testicular Cancer, Thymus Cancer, Thyroid  
Cancer, Transitional-Cell-Cancer-(bladder), Transitional-Cell-Cancer-(renal-pelvis-/

ureter), Trophoblastic Cancer, Urethral Cancer, Urinary System Cancer, Uroplakins, Uterine sarcoma, Uterus Cancer, Vaginal Cancer, Vulva Cancer, Waldenstrom's-Macroglobulinemia, Wilms' Tumor.

- 5 The compounds of the invention can be utilized in pharmaceutical compositions by adding an effective amount of a compound to a suitable pharmaceutically acceptable diluent or carrier. Use of the compounds and methods of the invention may also be useful prophylactically.
- 10 As is known in the art, a nucleoside is a base-sugar combination. The base portion of the nucleoside is normally a heterocyclic base. The two most common classes of such heterocyclic bases are the purines and the pyrimidines. Nucleotides are nucleosides that further include a phosphate group covalently linked to the sugar portion of the nucleoside. For those nucleosides that include a pentofuranosyl sugar, the phosphate group can be  
15 linked to either the 2', 3' or 5' hydroxyl moiety of the sugar. In forming oligonucleotides, the phosphate groups covalently link adjacent nucleosides to one another to form a linear polymeric compound. In turn, the respective ends of this linear polymeric compound can be further joined to form a circular compound, however, linear compounds are generally preferred. In addition, linear compounds may have internal nucleotide complementarity  
20 and may therefore fold in a manner as to produce a fully or partially double-stranded compound. Within oligonucleotides, the phosphate groups are commonly referred to as forming the internucleoside backbone of the oligonucleotide. The normal linkage or backbone of RNA and DNA is a 3' to 5' phosphodiester linkage.
- 25 Specific examples of preferred antisense or sense compounds useful in this invention include oligonucleotides containing modified backbones or non-natural internucleoside linkages. As defined in this specification, oligonucleotides having modified backbones include those that retain a phosphorus atom in the backbone and those that do not have a phosphorus atom in the backbone. For the purposes of this specification, and as sometimes  
30 referenced in the art, modified oligonucleotides that do not have a phosphorus atom in their internucleoside backbone can also be considered to be oligonucleosides.

Preferred modified oligonucleotide backbones containing a phosphorus atom therein include, for example, phosphorothioates, chiral phosphorothioates, phosphorodithioates, phosphotriesters, aminoalkylphosphotriesters, methyl and other alkyl phosphonates including 3'-alkylene phosphonates, 5'-alkylene phosphonates and chiral phosphonates, phosphinates, phosphoramidates including 3'-amino phosphoramidate and aminoalkylphosphoramidates, thionophosphoramidates, thionoalkylphosphonates, thionoalkylphosphotriesters, selenophosphates and boranophosphates having normal 3'-5' linkages, 2'-5' linked analogs of these, and those having inverted polarity wherein one or more internucleotide linkages is a 3' to 3', 5' to 5' or 2' to 2' linkage. Preferred oligonucleotides having inverted polarity comprise a single 3' to 3' linkage at the 3'-most internucleotide linkage i.e. a single inverted nucleoside residue which may be abasic (the nucleotide is missing or has a hydroxyl group in place thereof). Various salts, mixed salts and free acid forms are also included.

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Representative United States patents that teach the preparation of the above phosphorus-containing linkages include, but are not limited to, U.S. Patent Numbers: 3,687,808; 4,469,863; 4,476,301; 5,023,243; 5,177,196; 5,188,897; 5,264,423; 5,276,019; 5,278,302; 5,286,717; 5,321,131; 5,399,676; 5,405,939; 5,453,496; 5,455,233; 5,466,677; 5,476,925; 20 5,519,126; 5,536,821; 5,541,306; 5,550,111; 5,563,253; 5,571,799; 5,587,361; 5,194,599; 5,565,555; 5,527,899; 5,721,218; 5,672,697 and 5,625,050.

Preferred modified oligonucleotide backbones that do not include a phosphorus atom therein have backbones that are formed by short chain alkyl or cycloalkyl internucleoside linkages, mixed heteroatom and alkyl or cycloalkyl internucleoside linkages, or one or more short chain heteroatomic or heterocyclic internucleoside linkages. These include those having morpholino linkages (formed in part from the sugar portion of a nucleoside); siloxane backbones; sulfide, sulfoxide and sulfone backbones; formacetyl and thioformacetyl backbones; methylene formacetyl and thioformacetyl backbones; riboacetyl 25 backbones; alkene containing backbones; sulfamate backbones; methyleneimino and methylenehydrazino backbones; sulfonate and sulfonamide backbones; amide backbones;

and others having mixed N, O, S and CH<sub>2</sub> component parts.

- Representative United States patents that teach the preparation of the above oligonucleosides include, but are not limited to, U.S. Patent Numbers: 5,034,506; 5,166,315; 5,185,444; 5,214,134; 5,216,141; 5,235,033; 5,264,562; 5,264,564; 5,405,938; 5,434,257; 5,466,677; 5,470,967; 5,489,677; 5,541,307; 5,561,225; 5,596,086; 5,602,240; 5,610,289; 5,602,240; 5,608,046; 5,610,289; 5,618,704; 5,623,070; 5,663,312; 5,633,360; 5,677,437; 5,792,608; 5,646,269 and 5,677,439.
- 10 In other preferred oligonucleotide mimetics, both the sugar and the internucleoside linkage (i.e. the backbone), of the nucleotide units are replaced with novel groups. The nucleotide units are maintained for hybridization with an appropriate target nucleic acid. One such compound, an oligonucleotide mimetic that has been shown to have excellent hybridization properties, is referred to as a peptide nucleic acid (PNA). In PNA compounds, the sugar-backbone of an oligonucleotide is replaced with an amide containing backbone, in particular an aminoethylglycine backbone. The nucleotides are retained and are bound directly or indirectly to aza nitrogen atoms of the amide portion of the backbone. Representative United States patents that teach the preparation of PNA compounds include, but are not limited to, U.S. Patent Numbers: 5,539,082; 5,714,331; 20 and 5,719,262. Further teaching of PNA compounds can be found in Nielsen *et al.*, *Science* 254: 1497-1500, 1991.

Preferred embodiments of the present invention are oligonucleotides with phosphorothioate backbones and oligonucleosides with heteroatom backbones, and in particular -CH<sub>2</sub>-NH-O-CH<sub>2</sub>-, -CH<sub>2</sub>-N(CH<sub>3</sub>)-O-CH<sub>2</sub>- [known as a methylene (methylimino) or MMI backbone], -CH<sub>2</sub>-O-N(CH<sub>3</sub>)-CH<sub>2</sub>-, -CH<sub>2</sub>-N(CH<sub>3</sub>)-N(CH<sub>3</sub>)-CH<sub>2</sub>- and -O-N(CH<sub>3</sub>)-CH<sub>2</sub>-CH<sub>2</sub>- [wherein the native phosphodiester backbone is represented as -O-P-O-CH<sub>2</sub>-] of the above referenced U.S. Patent Number: 5,489,677, and the amide backbones of the above referenced U.S. Patent Number: 5,602,240. Also preferred are oligonucleotides 30 having morpholino backbone structures of the above-referenced U.S. Patent Number: 5,034,506.

Modified oligonucleotides may also contain one or more substituted sugar moieties. Preferred oligonucleotides comprise one of the following at the 2' position: OH; F; O-, S-, or N-alkyl; O-, S-, or N-alkenyl; O-, S- or N-alkynyl; or O-alkyl-O-alkyl, wherein the 5 alkyl, alkenyl and alkynyl may be substituted or unsubstituted C<sub>1</sub> to C<sub>10</sub> alkyl or C<sub>2</sub> to C<sub>10</sub> alkenyl and alkynyl. Particularly preferred are O[(CH<sub>2</sub>)<sub>n</sub>O]<sub>m</sub>CH<sub>3</sub>, O(CH<sub>2</sub>)<sub>n</sub>OCH<sub>3</sub>, O(CH<sub>2</sub>)<sub>n</sub>NH<sub>2</sub>, O(CH<sub>2</sub>)<sub>n</sub>CH<sub>3</sub>, O(CH<sub>2</sub>)<sub>n</sub>ONH<sub>2</sub>, and O(CH<sub>2</sub>)<sub>n</sub>ON[(CH<sub>2</sub>)<sub>n</sub>CH<sub>3</sub>]<sub>2</sub>, where n and m are from 1 to about 10. Other preferred oligonucleotides comprise one of the following at the 2' position: C<sub>1</sub> to C<sub>10</sub> lower alkyl, substituted lower alkyl, alkenyl, alkynyl, alkaryl, 10 aralkyl, O-alkaryl or O-aralkyl, SH, SCH<sub>3</sub>, OCN, Cl, Br, CN, CF<sub>3</sub>, OCF<sub>3</sub>, SOCH<sub>3</sub>, SO<sub>2</sub>CH<sub>3</sub>, ONO<sub>2</sub>, NO<sub>2</sub>, N<sub>3</sub>, NH<sub>2</sub>, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, an RNA cleaving group, a reporter group, an intercalator, a group for improving the pharmacokinetic properties of an oligonucleotide, or a group for improving the pharmacodynamic properties of an oligonucleotide, and other substituents 15 having similar properties. A preferred modification includes 2'-methoxyethoxy (2'-O-CH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>, also known as 2'-O-(2-methoxyethyl) or 2'-MOE) (Martin *et al.*, *Helv. Chim. Acta*, 78: 486-504, 1995) i.e., an alkoxyalkoxy group. A further preferred modification includes 2'-dimethylaminoxyethoxy, i.e., a O(CH<sub>2</sub>)<sub>2</sub>ON(CH<sub>3</sub>)<sub>2</sub> group, also known as 2'-DMAOE, as described in examples hereinbelow, and 2'- 20 dimethylaminoethoxyethoxy (also known in the art as 2'-O-dimethyl-amino-ethoxy-ethyl or 2'-DMAEOE), i.e., 2'-O-CH<sub>2</sub>-O-CH<sub>2</sub>-N(CH<sub>3</sub>)<sub>2</sub>, also described in examples hereinbelow.

Other preferred modifications include 2'-methoxy (2'-O-CH<sub>3</sub>), 2'-aminopropoxy (2'-OCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>NH<sub>2</sub>), 2'-allyl (2'-CH<sub>2</sub>-CH=CH<sub>2</sub>), 2'-O-allyl (2'-O-CH<sub>2</sub>-CH=CH<sub>2</sub>) and 2'- 25 fluoro (2'-F). The 2'-modification may be in the arabino (up) position or ribo (down) position. A preferred 2'-arabino modification is 2'-F. Similar modifications may also be made at other positions on the oligonucleotide, particularly the 3' position of the sugar on the 3' terminal nucleotide or in 2'-5' linked oligonucleotides and the 5' position of 5' terminal nucleotide. Oligonucleotides may also have sugar mimetics such as cyclobutyl 30 moieties in place of the pentofuranosyl sugar. Representative United States patents that teach the preparation of such modified sugar structures include, but are not limited to, U.S.

Patent Numbers: 4,981,957; 5,118,800; 5,319,080; 5,359,044; 5,393,878; 5,446,137; 5,466,786; 5,514,785; 5,519,134; 5,567,811; 5,576,427; 5,591,722; 5,597,909; 5,610,300; 5,627,053; 5,639,873; 5,646,265; 5,658,873; 5,670,633; 5,792,747; and 5,700,920.

- 5 A further preferred modification of the sugar includes Locked Nucleic Acids (LNAs) in which the 2'-hydroxyl group is linked to the 3' or 4' carbon atom of the sugar ring, thereby forming a bicyclic sugar moiety. The linkage is preferably a methylene (-CH<sub>2</sub>-)<sub>n</sub> group bridging the 2' oxygen atom and the 4' carbon atom wherein n is 1 or 2. LNAs and preparation thereof are described in WO 98/39352 and WO 99/14226.

10

- Oligonucleotides may also include nucleotide (often referred to in the art simply as "base") modifications or substitutions. As used herein, "unmodified" or "natural" nucleotides include the purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T), cytosine (C) and uracil (U). Modified nucleotides include other synthetic and natural 15 nucleotides such as 5-methylcytosine (5-me-C), 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-methyl and other alkyl derivatives of adenine and guanine, 2-propyl and other alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-halouracil and cytosine, 5-propynyl (-C≡C-CH<sub>3</sub>) uracil and cytosine and other alkynyl derivatives of pyrimidine bases, 6-azo uracil, cytosine and thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-20 hydroxyl and other 8-substituted adenines and guanines, 5-halo particularly 5-bromo, 5-trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylguanine and 7-methyladenine, 2-F-adenine, 2-amino-adenine, 8-azaguanine and 8-azaadenine, 7-deazaguanine and 7-deazaadenine and 3-deazaguanine and 3-deazaadenine. Further 25 modified nucleotides include tricyclic pyrimidines such as phenoxazine cytidine(1H-pyrimido[5,4-b][1,4]benzoxazin-2(3H)-one), phenothiazine cytidine (1H-pyrimido[5,4-b][1,4]benzothiazin-2(3H)-one), G-clamps such as a substituted phenoxazine cytidine (e.g. 9-(2-aminoethoxy)-H-pyrimido[5,4-b][1,4]benzoxazin-2(3H)-one), carbazole cytidine (2H-pyrimido[4,5-b]indol-2-one), pyridoindole cytidine (H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-2-one). Modified nucleotides may also include those in which the purine or pyrimidine base is replaced with other heterocycles, for example 7-deaza-adenine, 7-

- deazaguanosine, 2-aminopyridine and 2-pyridone. Further nucleotides include those disclosed in United States Patent No. 3,687,808, those disclosed in *The Concise Encyclopedia Of Polymer Science And Engineering*, pages 858-859, Kroschwitz, J.I., ed. John Wiley & Sons, 1990, those disclosed by Englisch *et al.*, *Angewandte Chemie*, 5 International Edition, 30: 613, 1991, and those disclosed by Sanghvi, Y.S., Chapter 15, *Antisense Research and Applications*, pages 289-302, Crooke, S.T. and Lebleu, B., ed., CRC Press, 1993. Certain of these nucleotides are particularly useful for increasing the binding affinity of the compounds of the invention. These include 5-substituted pyrimidines, 6-azapyrimidines and N-2, N-6 and O-6 substituted purines, including 2- 10 aminopropyladenine, 5-propynyluracil and 5-propynylcytosine. 5-methylcytosine substitutions have been shown to increase nucleic acid duplex stability by 0.6-1.2 °C and are presently preferred base substitutions, even more particularly when combined with 2'-O-methoxyethyl sugar modifications.
- 15 Representative United States patents that teach the preparation of certain of the above noted modified nucleotides as well as other modified nucleotides include, but are not limited to, the above noted U.S. Patent Number: 3,687,808, as well as U.S. Patent Numbers: 4,845,205; 5,130,302; 5,134,066; 5,175,273; 5,367,066; 5,432,272; 5,457,187; 5,459,255; 5,484,908; 5,502,177; 5,525,711; 5,552,540; 5,587,469; 5,594,121, 5,596,091; 20 5,614,617; 5,645,985; 5,830,653; 5,763,588; 6,005,096; and 5,681,941.

Another modification of the oligonucleotides of the invention involves chemically linking to the oligonucleotide one or more moieties or conjugates which enhance the activity, cellular distribution or cellular uptake of the oligonucleotide. These moieties or conjugates 25 can include conjugate groups covalently bound to functional groups such as primary or secondary hydroxyl groups. Conjugate groups of the invention include intercalators, reporter molecules, polyamines, polyamides, polyethylene glycols, polyethers, groups that enhance the pharmacodynamic properties of oligomers, and groups that enhance the pharmacokinetic properties of oligomers. Typical conjugate groups include cholesterol, 30 lipids, phospholipids, biotin, phenazine, folate, phenanthridine, anthraquinone, acridine, fluoresceins, rhodamines, coumarins, and dyes. Groups that enhance the

pharmacodynamic properties, in the context of this invention, include groups that improve uptake, enhance resistance to degradation, and/or strengthen sequence-specific hybridization with the target nucleic acid. Groups that enhance the pharmacokinetic properties, in the context of this invention, include groups that improve uptake,  
5 distribution, metabolism or excretion of the compounds of the present invention. Representative conjugate groups are disclosed in International Patent Application PCT/US92/09196, filed October 23, 1992, and U.S. Patent Number: 6,287,860, the entire disclosure of which are incorporated herein by reference. Conjugate moieties include but  
10 are not limited to lipid moieties such as a cholesterol moiety, cholic acid, a thioether, e.g., hexyl-S-tritylthiol, a thiocholesterol, an aliphatic chain, e.g., dodecandiol or undecyl residues, a phospholipid, e.g., di-hexadecyl-rac-glycerol or triethylammonium 1,2-di-O-hexadecyl-rac-glycero-3-H-phosphonate, a polyamine or a polyethylene glycol chain, or adamantan acetic acid, a palmityl moiety, or an octadecylamine or hexylamino-carbonyloxycholesterol moiety. Oligonucleotides of the invention may also be conjugated to active  
15 drug substances, for example, aspirin, warfarin, phenylbutazone, ibuprofen, suprofen, fenbufen, ketoprofen, (S)-(+)-pranoprofen, carprofen, dansylsarcosine, 2,3,5-triiodobenzoic acid, flufenamic acid, folinic acid, a benzothiadiazide, chlorothiazide, a diazepine, indomethacin, a barbiturate, a cephalosporin, a sulfa drug, an antidiabetic, an antibacterial or an antibiotic.  
20 Representative United States patents that teach the preparation of such oligonucleotide conjugates include, but are not limited to, U.S. Patent Numbers: 4,828,979; 4,948,882; 5,218,105; 5,525,465; 5,541,313; 5,545,730; 5,552,538; 5,578,717; 5,580,731; 5,580,731; 5,591,584; 5,109,124; 5,118,802; 5,138,045; 5,414,077; 5,486,603; 5,512,439; 5,578,718;  
25 5,608,046; 4,587,044; 4,605,735; 4,667,025; 4,762,779; 4,789,737; 4,824,941; 4,835,263; 4,876,335; 4,904,582; 4,958,013; 5,082,830; 5,112,963; 5,214,136; 5,082,830; 5,112,963; 5,214,136; 5,245,022; 5,254,469; 5,258,506; 5,262,536; 5,272,250; 5,292,873; 5,317,098; 5,371,241; 5,391,723; 5,416,203; 5,451,463; 5,510,475; 5,512,667; 5,514,785; 5,565,552;  
30 5,567,810; 5,574,142; 5,585,481; 5,587,371; 5,595,726; 5,597,696; 5,599,923; 5,599,928 and 5,688,941, certain of which are commonly owned with the instant application, and each of which is herein incorporated by reference.

It is not necessary for all positions in a given compound to be uniformly modified, and in fact more than one of the aforementioned modifications may be incorporated in a single compound or even at a single nucleoside within an oligonucleotide.

5

The present invention also includes antisense or sense compounds which are chimeric compounds. "Chimeric" antisense compounds or "chimeras", in the context of this invention, are antisense or sense compounds, particularly oligonucleotides, which contain two or more chemically distinct regions, each made up of at least one monomer unit, i.e., a 10 nucleotide in the case of an oligonucleotide compound. These oligonucleotides typically contain at least one region wherein the oligonucleotide is modified so as to confer upon the oligonucleotide increased resistance to nuclease degradation, increased cellular uptake, increased stability and/or increased binding affinity for the target nucleic acid. An additional region of the oligonucleotide may serve as a substrate for enzymes capable of 15 cleaving RNA:DNA or RNA:RNA hybrids. By way of example, RNase H is a cellular endonuclease which cleaves the RNA strand of an RNA:DNA duplex. Activation of RNase H, therefore, results in cleavage of the RNA target, thereby greatly enhancing the efficiency of oligonucleotide-mediated inhibition of gene expression. The cleavage of RNA:RNA hybrids can, in like fashion, be accomplished through the actions of 20 endoribonucleases, such as RNaseL which cleaves both cellular and viral RNA. Cleavage of the RNA target can be routinely detected by gel electrophoresis and, if necessary, associated nucleic acid hybridization techniques known in the art.

25

Chimeric antisense or sense compounds of the invention may be formed as composite structures of two or more oligonucleotides, modified oligonucleotides, oligonucleosides and/or oligonucleotide mimetics as described above. Such compounds have also been referred to in the art as hybrids or gapmers. Representative United States patents that teach the preparation of such hybrid structures include, but are not limited to, U.S. Patent Numbers: 5,013,830; 5,149,797; 5,220,007; 5,256,775; 5,366,878; 5,403,711; 5,491,133; 30 5,565,350; 5,623,065; 5,652,355; 5,652,356; and 5,700,922.

The compounds of the invention may also be admixed, encapsulated, conjugated or otherwise associated with other molecules, molecule structures or mixtures of compounds, as for example, liposomes, receptor-targeted molecules, oral, rectal, topical or other formulations, for assisting in uptake, distribution and/or absorption. Representative United

- 5 States patents that teach the preparation of such uptake, distribution and/or absorption-assisting formulations include, but are not limited to, U.S. Patent Numbers: 5,108,921; 5,354,844; 5,416,016; 5,459,127; 5,521,291; 5,543,158; 5,547,932; 5,583,020; 5,591,721; 4,426,330; 4,534,899; 5,013,556; 5,108,921; 5,213,804; 5,227,170; 5,264,221; 5,356,633; 5,395,619; 5,416,016; 5,417,978; 5,462,854; 5,469,854; 5,512,295; 5,527,528; 5,534,259;
- 10 5,543,152; 5,556,948; 5,580,575; and 5,595,756, each of which is herein incorporated by reference.

The antisense or sense compounds of the invention encompass any pharmaceutically acceptable salts, esters, or salts of such esters, or any other compound which, upon 15 administration to an animal, including a human, is capable of providing (directly or indirectly) the biologically active metabolite or residue thereof. Accordingly, for example, the disclosure is also drawn to prodrugs and pharmaceutically acceptable salts of the compounds of the invention, pharmaceutically acceptable salts of such prodrugs, and other bioequivalents.

- 20 25 The term "prodrug" indicates a therapeutic agent that is prepared in an inactive form that is converted to an active form (i.e., drug) within the body or cells thereof by the action of endogenous enzymes or other chemicals and/or conditions. In particular, prodrug versions of the oligonucleotides of the invention are prepared as SATE [(S-acetyl-2-thioethyl) phosphate] derivatives according to the methods disclosed in WO 93/24510 to Gosselin *et al.*, published December 9, 1993 or in WO 94/26764 and U.S. Patent Number: 5,770,713 to Imbach *et al.*.

- 30 The term "pharmaceutically acceptable salts" refers to physiologically and pharmaceutically acceptable salts of the compounds of the invention: i.e., salts that retain the desired biological activity of the parent compound and do not impart undesired

toxicological effects thereto. For oligonucleotides, preferred examples of pharmaceutically acceptable salts and their uses are further described in U.S. Patent Number: 6,287,860.

The present invention also includes pharmaceutical compositions and formulations which  
5 include the antisense or sense compounds of the invention. The pharmaceutical compositions of the present invention may be administered in a number of ways depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration may be topical (including ophthalmic and to mucous membranes including vaginal and rectal delivery), pulmonary, e.g., by inhalation or insufflation of powders or  
10 aerosols, including by nebulizer; intratracheal, intranasal, epidermal and transdermal), oral or parenteral. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal or intramuscular injection or infusion; or intracranial, e.g., intrathecal or intraventricular, administration. Oligonucleotides with at least one 2'-O-methoxyethyl modification are believed to be particularly useful for oral administration. Pharmaceutical  
15 compositions and formulations for topical administration may include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable. Coated condoms, gloves and the like may also be useful.

20

The pharmaceutical formulations of the present invention, which may conveniently be presented in unit dosage form, may be prepared according to conventional techniques well known in the pharmaceutical industry. Such techniques include the step of bringing into association the active ingredients with the pharmaceutical carrier(s) or excipient(s). In  
25 general, the formulations are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

The compositions of the present invention may be formulated into any of many possible  
30 dosage forms such as, but not limited to, tablets, capsules, gel capsules, liquid syrups, soft gels, suppositories, and enemas. The compositions of the present invention may also be

formulated as suspensions in aqueous, non-aqueous or mixed media. Aqueous suspensions may further contain substances which increase the viscosity of the suspension including, for example, sodium carboxymethylcellulose, sorbitol and/or dextran. The suspension may also contain stabilizers.

5

Pharmaceutical compositions of the present invention include, but are not limited to, solutions, emulsions, foams and liposome-containing formulations. The pharmaceutical compositions and formulations of the present invention may comprise one or more penetration enhancers, carriers, excipients or other active or inactive ingredients.

10

Emulsions are typically heterogenous systems of one liquid dispersed in another in the form of droplets usually exceeding 0.1 µm in diameter. Emulsions may contain additional components in addition to the dispersed phases, and the active drug which may be present as a solution in either the aqueous phase, oily phase or itself as a separate phase.

15

Microemulsions are included as an embodiment of the present invention. Emulsions and their uses are well known in the art and are further described in U.S. Patent Number: 6,287,860, which is incorporated herein in its entirety.

20

Formulations of the present invention include liposomal formulations. As used in the present invention, the term "liposome" means a vesicle composed of amphiphilic lipids arranged in a spherical bilayer or bilayers. Liposomes are unilamellar or multilamellar vesicles which have a membrane formed from a lipophilic material and an aqueous interior that contains the composition to be delivered. Cationic liposomes are positively charged liposomes which are believed to interact with negatively charged DNA molecules to form a stable complex. Liposomes that are pH-sensitive or negatively-charged are believed to entrap DNA rather than complex with it. Both cationic and noncationic liposomes have been used to deliver DNA to cells.

25

Liposomes also include "sterically stabilized" liposomes, a term which, as used herein, refers to liposomes comprising one or more specialized lipids that, when incorporated into liposomes, result in enhanced circulation lifetimes relative to liposomes lacking such

specialized lipids. Examples of sterically stabilized liposomes are those in which part of the vesicle-forming lipid portion of the liposome comprises one or more glycolipids or is derivatized with one or more hydrophilic polymers, such as a polyethylene glycol (PEG) moiety. Liposomes and their uses are further described in U.S. Patent Number: 6,287,860,  
5 which is incorporated herein in its entirety.

The pharmaceutical formulations and compositions of the present invention may also include surfactants. The use of surfactants in drug products, formulations and in emulsions is well known in the art. Surfactants and their uses are further described in U.S. Patent  
10 Number: 6,287,860.

In one embodiment, the present invention employs various penetration enhancers to effect the efficient delivery of nucleic acids, particularly oligonucleotides. In addition to aiding the diffusion of non-lipophilic drugs across cell membranes, penetration enhancers also  
15 enhance the permeability of lipophilic drugs. Penetration enhancers may be classified as belonging to one of five broad categories, *i.e.*, surfactants, fatty acids, bile salts, chelating agents, and non-chelating non-surfactants. Penetration enhancers and their uses are further described in U.S. Patent Number: 6,287,860.

20 One of skill in the art will recognize that formulations are routinely designed according to their intended use, *i.e.* route of administration.

Preferred formulations for topical administration include those in which the oligonucleotides of the invention are in admixture with a topical delivery agent such as  
25 lipids, liposomes, fatty acids, fatty acid esters, steroids, chelating agents and surfactants. Preferred lipids and liposomes include neutral (e.g. dioleoylphosphatidyl DOPE ethanolamine, dimyristoylphosphatidyl choline DMPC, distearoylphosphatidyl choline) negative (e.g. dimyristoylphosphatidyl glycerol DMPG) and cationic (e.g. dioleoyltetramethylaminopropyl DOTAP and dioleoylphosphatidyl ethanolamine  
30 DOTMA).

For topical or other administration, oligonucleotides of the invention may be encapsulated within liposomes or may form complexes thereto, in particular to cationic liposomes. Alternatively, oligonucleotides may be complexed to lipids, in particular to cationic lipids. Preferred fatty acids and esters, pharmaceutically acceptable salts thereof, and their uses  
5 are further described in U.S. Patent Number: 6,287,860.

Compositions and formulations for oral administration include powders or granules, microparticulates, nanoparticulates, suspensions or solutions in water or non-aqueous media, capsules, gel capsules, sachets, tablets or minitablets. Thickeners, flavoring agents,  
10 diluents, emulsifiers, dispersing aids or binders may be desirable. Preferred oral formulations are those in which oligonucleotides of the invention are administered in conjunction with one or more penetration enhancers surfactants and chelators. Preferred surfactants include fatty acids and/or esters or salts thereof, bile acids and/or salts thereof. Preferred bile acids/salts and fatty acids and their uses are further described in U.S. Patent  
15 Number: 6,287,860, which is incorporated herein in its entirety. Also preferred are combinations of penetration enhancers, for example, fatty acids/salts in combination with bile acids/salts. A particularly preferred combination is the sodium salt of lauric acid, capric acid and UDCA. Further penetration enhancers include polyoxyethylene-9-lauryl ether, polyoxyethylene-20-cetyl ether. Oligonucleotides of the invention may be delivered  
20 orally, in granular form including sprayed dried particles, or complexed to form micro or nanoparticles. Oligonucleotide complexing agents and their uses are further described in U.S. Patent Number: 6,287,860.

Compositions and formulations for parenteral, intrathecal or intraventricular administration  
25 may include sterile aqueous solutions which may also contain buffers, diluents and other suitable additives such as, but not limited to, penetration enhancers, carrier compounds and other pharmaceutically acceptable carriers or excipients.

Certain embodiments of the invention provide pharmaceutical compositions containing one  
30 or more oligomeric compounds and one or more other chemotherapeutic agents which function by a non-antisense mechanism. Examples of such chemotherapeutic agents

- 100 -

include but are not limited to cancer chemotherapeutic drugs such as daunorubicin, daunomycin, dactinomycin, doxorubicin, epirubicin, idarubicin, esorubicin, bleomycin, mafosfamide, ifosfamide, cytosine arabinoside, bis-chloroethylnitrosurea, busulfan, mitomycin C, actinomycin D, mithramycin, prednisone, hydroxyprogesterone, 5 testosterone, tamoxifen, dacarbazine, procarbazine, hexamethylmelamine, pentamethylmelamine, mitoxantrone, amsacrine, chlorambucil, methylcyclohexylnitrosurea, nitrogen mustards, melphalan, cyclophosphamide, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-azacytidine, hydroxyurea, deoxycoformycin, 4-hydroxyperoxycyclophosphoramidate, 5-fluorouracil (5-FU), 5-fluorodeoxyuridine (5-FUDR), methotrexate (MTX), colchicine, taxol, vincristine, vinblastine, etoposide (VP-16), trimetrexate, irinotecan, topotecan, gemcitabine, teniposide, cisplatin and diethylstilbestrol (DES). When used with the compounds of the invention, such chemotherapeutic agents may be used individually (e.g., 5-FU and oligonucleotide), sequentially (e.g., 5-FU and oligonucleotide for a period of time followed by MTX and oligonucleotide), or in combination with one or more other such chemotherapeutic agents (e.g., 5-FU, MTX and oligonucleotide, or 5-FU, radiotherapy and oligonucleotide). Anti-inflammatory drugs, including but not limited to nonsteroidal anti-inflammatory drugs and corticosteroids, and antiviral drugs, including but not limited to ribivirin, vidarabine, acyclovir and ganciclovir, may also be combined in compositions of the invention. Combinations of antisense or sense compounds and other non-antisense drugs are also within the scope of this invention. Two or more combined compounds may be used together or sequentially.

In another related embodiment, compositions of the invention may contain one or more antisense or sense compounds, particularly oligonucleotides, targeted to a first nucleic acid and one or more additional antisense or sense compounds targeted to a second nucleic acid target. Alternatively, compositions of the invention may contain two or more antisense or sense compounds targeted to different regions of the same nucleic acid target. Numerous examples of antisense or sense compounds are known in the art. Two or more combined compounds may be used together or sequentially.

30

The formulation of therapeutic compositions and their subsequent administration (dosing)

is believed to be within the skill of those in the art. Dosing is dependent on severity and responsiveness of the disease state to be treated, with the course of treatment lasting from several days to several months, or until a cure is effected or a diminution of the disease state is achieved. Optimal dosing schedules can be calculated from measurements of drug  
5 accumulation in the body of the patient. Persons of ordinary skill can easily determine optimum dosages, dosing methodologies and repetition rates. Optimum dosages may vary depending on the relative potency of individual oligonucleotides, and can generally be estimated based on EC<sub>50</sub>s found to be effective in *in vitro* and *in vivo* animal models. In general, dosage is from 0.01 ug to 100 g per kg of body weight, and may be given once or  
10 more daily, weekly, monthly or yearly, or even once every 2 to 20 years. Persons of ordinary skill in the art can easily estimate repetition rates for dosing based on measured residence times and concentrations of the drug in bodily fluids or tissues. Following successful treatment, it may be desirable to have the patient undergo maintenance therapy to prevent the recurrence of the disease state, wherein the oligonucleotide is administered  
15 in maintenance doses, ranging from 0.01 ug to 100 g per kg of body weight, once or more daily, to once every 20 years. Examples of effective amounts include 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 2, 3, 4, 5, 6,  
7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31,  
32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55,  
20 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79,  
80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 and 100g/kg  
body weight.

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## EXAMPLE 1

### *Cell line*

The MDA-MB 231 human breast cancer cell line was obtained from American tissue culture collection (Rockville, USA) and cultivated at 37°C in 100% (v/v) air, and maintained in Leibovitz L-15 Medium (Sigma, St Louis, Mo., USA), supplemented with 10% foetal calf serum (CSL, Melbourne, Australia) and antibiotic/antimycotic reagents (Sigma, St Louis, Mo., USA).

10

## EXAMPLE 2

### *Isolation of the cDNA for human HAS2 and construction of an antisense expression vector*

The cDNA for human HAS2 was generated by designing gene specific primers from the published sequence of Watanabe and Yamaguchi (1996; Genbank accession no. U54804) and consisted of the following primers: sense 5'>GAGCTGAACAAGATGCATTGTGAGAGC (SEQ ID NO:1) and antisense 5'GACATGGTGCTT-GATGTATGATCTTCCAT (SEQ ID NO:2). Total RNA harvested from exponentially dividing human dermal fibroblasts was used as the template for RT-PCR to generate a 1.7kb cDNA fragment of HAS2, which was cloned directly into pGEM-T vector (Promega Corporation, Madisom, USA). The cDNA for HAS2 was subsequently subcloned into the pCI-Neo expression vector (Promega Corporation, Madisom, USA) and isolated clones containing the insert in the antisense orientation were identified by restriction endonuclease mapping and automated sequencing.

25

## EXAMPLE 3

### *Transfection of human ASHAS2 and mock into MDA-MB 231 human breast caner cells*

The ASHAS2-pCI-Neo construct and pCI-neo vector were transfected into human MDA-MB 231 breast cells using Lipofectamine plus reagent (Gibco life technologies, USA) according to the manufacture's instructions. Prior to commencing studies transfected cells

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were selected for at least one month in the presence of 500µg/mL G418 antibiotic. Transfected cells were selected for at least one month in the presence of 500µg/mL G418 antibiotic. Resistant colonies were then harvested and established as stable cell lines.

5

#### EXAMPLE 4

##### *Detecting the incorporation of the stable transfection into the genome*

PCR on purified genomic DNA isolated from ASHAS2-pCINeo transfectants was performed to confirm the incorporation of the antisense construct into the genome. In  
10 brief, a gene specific primer for pCINeo: 5'-GCACAGATGCGTAAGGAG-3' (SEQ ID NO:3) was used in combination with two specific HAS2 primers of the following sequence: GSP2 sense 5'-GCTGTGTACATGACCTCGCGCTTGCCGCC-3' (SEQ ID NO:4) and GSP4 sense, 5'-GGCGGGAAAGTAAACTCGAC-3' (SEQ ID NO:5). When used in the following combination; pCIneo/GSP2 and pCIneo/GSP4 expected size  
15 products of 1443 and 2223bp were amplified respectively.

#### EXAMPLE 5

##### *Quantification of mRNA for HAS1, 2 and 3*

20 Real time PCR was used to quantitate the relative mRNA levels of HAS1, HAS2, and HAS3 in parental, mock and ASHAS2 transfected cells using gene specific primers and an internal oligonucleotide probe. In brief, total RNA was purified from experimental cells using Rneasy (Qaigen, Melbourne, Australia) which was then used to generate single stranded cDNA by incubating 2µg RNA with 0.5µg/µL random primers and superscript  
25 reverse transcriptase. For quantitative real time PCR gene specific primers for each HAS isoform and an internal oligonucleotide probe were used. In brief, the primers consisted of the following: HAS1, sense, 5' CCTGCATCAGCGGTCTA 3' (SEQ ID NO:6); HAS1 antisense, 5' GCCGGTCA-TCCCCAAAAG 3' (SEQ ID NO:7); HAS1 probe, 5'  
AACCTCTTGCAGCAGTTCTTGAGGCC 3' (SEQ ID NO:8); HAS2 sense, 5'  
30 CAGTCCTGGCTTCGAGCAG 3' (SEQ ID NO:9), HAS2 antisense, 5' TTGGGAGAAAAGTCTTGGCT 3' (SEQ ID NO:10); HAS2 probe, 5'

CCATTGAACCAG-AGACTTGAAACAGCCC 3' (SEQ ID NO:11); HAS3 sense, 5'  
TTGCACTGTGGTCGTCAACTT 3' (SEQ ID NO:12), HAS3 antisense, 5'  
GTCGAGGTCAAACGTTGTGAG 3' (SEQ ID NO:13), HAS3 probe, 5'  
TCAAATAAAAACAGGCAGGTACAGGTAGTGG 3' (SEQ ID NO:14); GAPDH  
5 sense, 5' AAGGTGAAGGTGGAGTCAAC 3' (SEQ ID NO:15), GAPDH antisense, 5'  
GAGTTAAA-GCAGCCCTGGTG 3' (SEQ ID NO:16), GAPDH probe, 5'  
TTTGGTCGTATTGGGCGCCTGG3' (SEQ ID NO:17). For HAS internal probes the  
reporter dye 6-carboxylfluorescein (6-FAM) and quencher 6-carboxytetramethyl  
rhodamine (TAMRA) were labelled at the 5' and 3' respectively.. For GAPDH internal  
10 probes the reporter 6-FAM was substituted with VIC™ (Applied Biosystems California,  
USA). The PCR reaction was performed in a final volume of 30µL and consisted of 1×  
Taqman reaction mix, 6µM of HAS forward and reverse primer, 1.5µM of probe, 1µM of  
each GAPDH primer and 500nM of GAPDH probe. PCR amplification was by  
denaturation for 10 minutes at 95°C followed by annealing for 2 minutes at 50°C followed  
15 by 40 cycles of 15 seconds at 95°C and 1 minute at 60°C. Thermocycling and fluorescence  
measurement were performed in a ABI Prism 7700 sequence detection system (Applied  
Biosystems, California, USA). To allow comparison between samples the relative  
hyaluronan synthase signals were normalised with internal GAPDH control measurements.

20

## EXAMPLE 6

### *Characterization of hyaluronidase gene expression*

To determine the state of hyaluronidase gene expression for HYAL1,2 and 3, RT-PCR was  
performed on total RNA extracted from experimental cells harvested at 80 and 100%  
25 confluence. The gene specific primer sets were designed from sequences retrieved from  
GenBank and consisted of: HYAL1 (GenBank accession no. NM007312) sense, 5'-  
GCACAGGGAAAGTCACAGATGTATGTGC-3' (SEQ ID NO:18); HYAL1 antisense, 5'-  
CCACTGGTCACGTTCAAGGATGAAG-3' (SEQ ID NO:19); HYAL2 (GenBank  
accession no. NM003773) sense 5'-GATGTGTATCGCC-GGTTATCACGCC-3' (SEQ ID  
30 NO:20); HYAL2 antisense 5'-CGTAGACTGGGAG-TGCATGGTTGGC-3' (SEQ ID  
NO:21); HYAL3 (GenBank accession no. NM003549) sense, 5'-

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GCACTGATGGAGGATACGCTGCG-3' (SEQ ID NO:22); HYAL3 antisense, 5'-GCTGGTGAUTG-CAGGCCATCGCTGC-3' (SEQ ID NO:23). Amplified sequences were visualised by agarose gel electrophoresis containing ethidium bromide and identity confirmed by automated DNA sequencing.

5

### EXAMPLE 7

#### *Cell proliferation assay*

Parental, mock and ASHAS2 transfectants were harvested at approximately 80%  
10 confluence and seeded in to 24-well plates at differing cell densities, ranging from  
5×10<sup>3</sup>cells to 9×10<sup>4</sup>cells/well. The rate of cell growth was then followed for 24, 48, 72,  
and 96hours after plating. All cell counts were determined using an automated Coulter  
counter.

15

### EXAMPLE 8

#### *Immunohistochemistry*

To allow immunodetection and comparison between parental, mock and ASHAS2-pCNeo  
transfected MDA-MB-231 cells specific antibodies to HAS2 and Hyal2 were kindly gifted  
20 from Dr Paraskevi Heldin and Dr Robert Stern respectively. Anti-human CD44 Clone  
DF1485 was purchased from DAKO (Denmark) and used according to manufacturers  
instructions. Cells were seeded into 8-well chamber slides at a density of 2×10<sup>4</sup> cells/well  
and grown for a further 24 hours at 37°C. The cells were fixed in Histochoice for 15  
minutes before blocking heterophile proteins by incubation in PBS containing 10%FCS.  
25 The primary antibodies were diluted to (cite concentration NOT dilution) in antibody  
diluent (PBS containing 1% human serum and 1% FCS) then incubated on slides for  
60min at room temperature. Endogenous peroxidase activity was blocked by immersion of  
slides in 0.3%H<sub>2</sub>O<sub>2</sub> in methanol for 20min prior to incubation with a peroxidase-  
conjugated rabbit anti-sheep secondary antiserum for 60min at RT. The  
30 immunocomplexes were visualised by applying 3,3'-Diaminobenzidine substrate (Sigma

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Fast DAB) for 5-10 minutes, then counterstained with haematoxylin, dehydrated and mounted.

#### EXAMPLE 9

5

##### *Cell cycle analysis by flow cytometry*

The transfected and control cells were seeded at  $2 \times 10^5$  cells/25cm<sup>2</sup> flask in the presence of 2mM thymidine and grown until 50% confluent. Cells were washed then returned to normal culture medium and harvested, by trypsinisation, at the following time points; 0h, 10 4h, 8h, 12h, 16h, 20h, 24h, 28h, 32h, and 36h then fixed in 95% ethanol for 2h at 4°C. Cells were pretreated with 100µg/mL RNAase (Sigma) and 50µg/ml propidium iodide (Sigma) for 30minutes at 37°C before determining the cell cycle stage in a FACS-Calibur™ analytical instrument (Becton Dickinson, San Jose, CA).

15

#### EXAMPLE 10

##### *Migration assay*

The Boyden chamber chemoattraction assay was performed as described previously (Thompson et al., 1992). Matrigel (50µg) was dried onto polycarbonate filters (12µm pore, PVP free, Nucleopore, Pleasanton, CA) and then reconstituted at 37°C. Normal growth media (L-15 medium) containing 0.1% bovine serum albumin (Miles Biochemicals, Kankakee, IL) was used as the chemo attractant. Cells were harvested in the logarithmic growth phase by trypsinisation, washed twice with serum-free L-15 medium containing 0.1% bovine serum albumin then seeded at 300,000 cells/1ml chamber, 25 and 70,000 cells/0.2ml chamber. Each experiment was performed in triplicate. Chambers were incubated in a humidified incubator at 37°C for 6 hours. To determine the population of cells which had traversed the matrigel, the filters were stained with Diff-Quik (American Scientific Products, McGaw PK., IL) then counted.

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### EXAMPLE 11

#### *Particle exclusion assay and cell morphology*

The HA-dependent pericellular matrix was visualised around breast cancer cells from  
5 control and transfected cultures by the exclusion of fixed human erythrocytes described by  
Clarris & Fraser (1968). Morphological differences as well as the particle exclusion assay  
in the control and transfected MDA-MB 231 cells were photographed on a Nikon Optiflou  
inverted phase contrast microscope (Nikon Company, Japan)  
24h and 60h after plating.

10

### EXAMPLE 12

#### *Effect of the HA production*

Cells were seeded at  $2.5 \times 10^5$ /cells in  $25\text{cm}^2$  culture flasks and incubated at  $37^\circ\text{C}$  for 24h,  
15 48h, 72h, 96h, 120h and 144h. At each time points cells were trypsinized and counted  
using an automated coulter counter. HA concentration in the harvested culture medium  
was determined using a hyaluronic acid binding protein (HABP) assay, with the standards  
and reaction buffer provided Coragenix Inc (Colorado, USA).

20

### EXAMPLE 13

#### *Size exclusion chromatography to determine MW of HA synthesized*

Cells were seeded at  $7.5 \times 10^5$  cells in  $75\text{cm}^2$  culture flasks and grown for 24h in complete  
medium supplemented with 5 $\mu\text{Ci}$  of D-[6- $^3\text{H}$ ]-Glucosamine hydrochloride. a. To  
25 determine the MW of  $^3\text{H}$ -HA in the medium, samples were subjected to size exclusion  
chromatography on a Sephadex G-100 SF. In brief, gel column (1.6m x 90m) were  
packed according to manufacturers instructions, equilibrated and eluted with phosphate  
buffer containing 0.2% (v/v) TX-100. The molecular weight of HA in the culture medium  
was calculated using linear regression of  $K_{av}$  versus HA of known molecular weights

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ranging from  $>1.67 \times 10^7$ ,  $K_{av}=0$  to  $4.4 \times 10^3$ ,  $K_{av}=1$ . Fraction range of column S-1000  $7 \times 10^4$  –  $1.7 \times 10^7$ Da.

#### EXAMPLE 14

5

##### *Mammary fat pad inoculation of MDA-MB 231 cells*

Parental, mock and ASHAS2 transfected cells were harvested in the logarithmic growth phase by scraping. Cells were resuspended to a final density of  $2 \times 10^6$  cells in L-15 medium supplemented with 0.1% glucose +/- Matrigel (v/vWHAT IS THE 10 PERCENTAGE?) then immediately injected into the mammary fat pad of 5 weeks old female CBA nude mice (n=11 does each treatment group consist of 11). Tumor growth was recorded twice weekly by measuring three perpendicular diameters (d1,d2,d3). Tumor volume was then calculated using the formula:  $(1/6)\pi (d_1 d_2 d_3)$ . On the day 84 mice were humanely killed and liver, kidneys, brain and lungs removed at autopsy and 15 stored at  $-20^{\circ}\text{C}$ . For histological examination half of the primary tumor was fixed in 4% formaldehyde and embedded in paraffin, then  $5\mu\text{m}$  sections from this tissue was examined by H&E staining. The remaining portion of the tumor was frozen at  $-20^{\circ}\text{C}$  until further analysis.

20

#### EXAMPLE 15

##### *DNA extraction from soft organs and quantification of metastasis of MDA-MD 231*

Quantitative Alu PCR was used to detect metastasis of MDA-MD 231 from the primary tumor to other organs collected at autopsy. In brief, DNA was extracted by griding 25 samples under liquid nitrogen and resuspending in a DNA lysis buffer. DNA was then purified using standard phenol-chloroform methodology followed by ethanol precipitation and reconstitution in TE buffer. The purified DNA was adjusted to a final concentration of 10ng/ $\mu\text{L}$  in TE buffer pH7.2, aliquoted and stored at  $-20^{\circ}\text{C}$  until analysis. To remove exogenous human DNA contamination the reaction mix was treated with 17U/ml nuclease 30 S7 (Roche) in the presence of 1mM CaCl<sub>2</sub> at  $37^{\circ}\text{C}$  for 24 hours prior to PCR. Quantitative

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Alu PCR was then performed on purified genomic DNA samples (10ng) in a GeneAmp 5700 Sequence Detection System (Applied Biosystems, Australia). In brief, each sample was tested in duplicate in a final reaction volume of 25µL consisting of 0.625U Taq DNA polymerase (Roche; Mannheim, Germany), 10mM Tris-HCl pH 8.3, 1.5mM MgCl<sub>2</sub>, 5 50mM KCl, 200µM dNTPs, 8% DMSO, 1µg/ml 6-carboxy-X-rhodamine (Molecular Probes; Eugene, Oregon USA), 1 in 40000 dilution of SYBR Green I (Molecular Probes) and 100nM of each Alu primer. Following an initial denaturation incubation at 95°C for 2 minutes, amplification occurred over 40 cycles, which consisted of denaturation at 95°C for 5seconds, annealing at 65°C for 60seconds, and extension at 75°C for 15seconds during 10 which the intensity of fluorescence was measured. A dissociation curve was then generated from 60°C to 95°C. On each 96-well reaction plate, a standard curve was prepared by serially diluting human DNA into mouse DNA which permitted the quantification of the tissue burden of human tumor cells in the mouse organs removed at autopsy.

15

#### EXAMPLE 16

##### *Transfection of antisense HAS2 in MDA-MB 231 transfected cells*

Incorporation of the antisense HAS2-pCINeo construct into the genome of MDA-MB 231 20 was confirmed by PCR analysis on highly purified DNA extracted from the transfected cells. When used in the following combination; pCINeo/GSP2 and pCINeo/GSP4 expected size products of 1443 and 2223bp were reproducibly amplified from stable clones harbouring the antisense HAS2 construct. Genomic DNA isolated from parental and mock transfected tested negative.

25

#### EXAMPLE 17

##### *Transfection with antisense HAS2 alters expression profiles of HAS and hyaluronidase genes in MDA-MB 231*

30 Endogenous levels of mRNA for HAS2 in parental cells were quantitated using real time PCR and compared with the values obtained from mock and antisense HAS2 transfected

cells. Concomitant to these experiments, HAS1 and HAS3 mRNA levels were also quantitated using real time PCR with HYAL1, 2 and 3 expression characterised by standard RT-PCR methodology. To allow comparison of real time HAS expression between transfected and parental cells the level of each mRNA quantitated was normalised 5 with respective internal GAPDH controls. The endogenous level of HAS2 mRNA expression in parental cells is shown in Figure 1a, which was slightly decreased in the mock transfectants. In contrast, mRNA expression in ASHAS2 transfected cells was increased 3- to 4-fold and 8- to 9-fold when compared with parental and mock transfectants cells respectively (Figure 1a). Moderate HAS3 expression was also detected 10 and was comparable in parental mock and antisense transfected cells Figure 1b. Consistant throughout this study was the expression of HAS1 in antisense transfectants which could not be detected in both parental cells and mock transfectants (Figure 1b).

Both parental and mock transfected control cultures stained positive for the HA receptor 15 CD44 and Hyal-2. The staining for CD44 in both controls was most evident in the plasma membrane with areas of intense focal membrane staining (Figure 1 panel E). No CD44 epitope reactivity could be detected in ASHAS2 transfectants (Figure 1 panel F). Similar observation were recorded for the reactivity with Hyal-2 antibody where control cultures stained positively, which localised to the plasma membrane and also appeared as 20 cytoplasmic vesicles whereas no reactivity could be detected in ASHAS2 transfectants. These results indicate that perturbation of functional CD44 and Hyal2, as observed in ASHAS2 transfectants, alter the catabolism of HA culminating in a significant increase in the amount HA in the culture medium.

25

## EXAMPLE 18

### *Characteristics of MDA MB 231 breast cancer cell in a tumor xenograft model*

Interestingly, antisense inhibition of HAS2 profoundly altered the expression of Hyal-1, 2 and 3 in MDA-MD 231. Hyal-3 could not be detected in both parental or mock 30 transfectants, which both expressed comparable levels of mRNA for Hyal-1 and to a much greater extent Hyal-2, which was also comparable between these two controls (Figure 2).

- In contrast, inhibition of HAS2 expression resulted in the down regulation of Hyal-2 mRNA to the point where it was not detectable even after 35 cycles of PCR. Hyal-1 expression in antisense transfectants was moderately increased when compared with both parental and mock controls and Hyal-3 was also detected in the antisense transfectants.
- 5 Thus by preventing the production of a functional HAS2 protein in the MDA-MD 231 cell line, Hyal-2 gene expression has been down regulated concomitant to the upregulation of HAS1 and Hyal3, genes that are not normally expressed in this cell line.
- 10 Immunohistochemistry with a specific HAS2 antibody was used to determine the extent of cell surface reactivity. Whereas both parental and mock transfected cells stained positively for HAS2 protein (Figure 1, panel B), which localised mostly to the plasma membrane, efficient blockage of translation in the antisense HAS2 transfectants was evidenced by the lack of immunoreactivity with the HAS2 antibody (Figure 1 panel C).
- 15 The molecular mass of HA synthesised by parental, mock and antisense transfected cells was determined by Sephadex G-100 size exclusion chromatography. The parental cell line synthesised three distinct molecular weights of HA estimated to be 3000 kDa, 40,000 and 100,000 Da respectively which reflects the products of the HAS isoforms expressed in the parental cell line, notably HAS2 and 3. Antisense HAS2 transfectants synthesised HA
- 20 which was eluted in the void volume that corresponds to a molecular weight  $>1.67 \times 10^7$ . Another fraction corresponding to a Mw of 100,000Da was also detected in the medium from antisense transfectants but the percentage of radioactive precursor incorporation was much less than that observed in the parental cell line (Figure 2). These elution profiles were shown to be 100% susceptible to digestion with *Streptomyces* hyaluronidase.
- 25 Antisense inhibition of HAS2 results in altered hyaluronan metabolism. Due to the altered HAS and HYAL gene expression in ASHAS2 MDA-MB 231 transfectants the amount of hyaluronan in cell contact culture medium was quantitated using an enzyme linked protein assay specific for HA. HA production was quantitated from samples collected in triplicate
- 30 at the same time points established in the proliferation assay. The data collected was graphed as HA synthesised (picogram per cell: pg/cell/day). Cell contact medium from

antisense HAS2-MDA-MB 231 transfecants contained a significantly greater amount of hyaluronan when compared with either parental cells or mock transfectants (Figure 3). On average ASHAS2 cultures synthesised 6.79pg of HA/cell/day over the duration of the experiment with one noticeable exception at 48hours where synthesis was increased to 5 12pg/cell/day. In contrast parental and mock transfectants synthesised approximately 1.1 and 1.4pgHA/cell/day respectively over the duration of the experiment. The exclusion of fixed erythrocytes was used to indirectly visualise the HA pericellular matrix in the ASHAS2 transfectants which was then compared with that observed in the parental or mock transfectants. In these experiments there was no evidence to suggest any gross 10 difference in the thickness of the pericellular matrix, which was comparable to that observed in control cultures (Figure 3b).

Throughout the experiments the morphology of the antisense transfected cells were compared with control cells. The ASHAS2 transfectants were readily distinguishable by 15 their morphology which was akin to cells undergoing mitosis and/or migration, that is, small rounded cells that were loosely adhered to the growth surface. Consistent throughout these observations was the decrease in cell number in ASHAS2 transfectants when compared with control cultures.

20

## EXAMPLE 19

### *HAS2 inhibition decreases breast cancer cell proliferation and migration in vitro*

To compare the effect of antisense inhibition of HAS2 during active cell growth, parental, mock and ASHAS2 transfected cells were seeded at identical sub-confluent densities and 25 at defined times were harvested and the total cell count estimated using a Coulter counter. In both control cultures a doubling of cell number every 24 hours was observed until the 72 hour sample point where cultures reached confluence (Figure 4). In contrast stable transfectants harbouring ASHAS2 cell growth was profoundly affected by the lack of a functional HAS2 protein. Specifically, ASHAS2 transfectants displayed a lag period of 30 approximately 24 hours to reach similar densities to that observed in control cultures at all subsequent time points where cell number was enumerated (Figure 4). Confluence in

ASHAS2 cultures occurred at approximately 96- to 120 hours of cell growth after seeding compared with 72 hours in both control cultures. These observations therefore highlight the importance of the co-ordinated expression of a functional HAS2 in cell proliferation.

5 Concomitant to these observations flow cytometric analysis was also performed on parental, mock and ASHAS2 transfectants to determine relative DNA content at defined time points after plating at sub-confluent densities (Figure 5). The percentage of the ASHAS2 transfected cells in the cell cycle phases G<sub>0</sub>/G<sub>1</sub>, S and G<sub>2</sub>/M 28 hours after plating were 80%, 0% and 9% respectively (Figure 5). In contrast the corresponding  
10 figures in the parental cells for cell cycle phases G<sub>0</sub>/G<sub>1</sub>, S and G<sub>2</sub>/M were 4%, 75% and 15% respectively (Figure 5). These results are consistent with the observation in the 'lag' period of 24 hours in the proliferation assay where antisense inhibition induced a transient delay of entry into S-phase by approximately 24 hours (Figure 5) thereby reinforcing the importance of HAS2 expression during cellular proliferation in cultures of MBA-MD-231.

15

The ability for cancer cells to migrate is a fundamental characteristic in highly metastatic cancer cells. To characterise the highly invasive characteristics of MDA MB-231 the chemoinvasion assay using the Boyden chamber was used. Migratory rates were then compared between parental, mock and ASHAS2 transfected MDA MB-231. Both parental  
20 and mock transfectants displayed typical migratory behaviour with 100% of cell population invading the matrigel onto the underlying filter (Figure 6). In contrast, stable transfectants harbouring antisense HAS2 resulted in 93% inhibition of migration when compared with either controls tested (Figure 6).

25

## EXAMPLE 20

### *HAS2 inhibition totally inhibits the growth and progression of primary and secondary breast cancer*

To examine the effects of antisense inhibition of HAS2 on tumor growth, parental, mock  
30 and ASHAS2 transfectants inoculated into the mammary fat pad of nude mice. Primary tumor growth was followed over a 12 week period following implantation after which the extent of metastasis to other organs detected using Alu PCR. Mice inoculated with

parental or mock transfected MDA MB 231 readily established primary tumors which were comparable in growth over the duration of the 12 week experiment (Figure 7). In contrast, however, mice inoculated with ASHAS2 transfectants did not establish primary tumors (Figure 7). In other experiments Matrigel was also included in the inoculation 5 medium used to ensure viability of injected ASHAS2 transfectants. Again, no primary tumor could be detected over the duration of the 12 week experiment (data not shown). As assessed by Alu PCR, metastasis was most prevalent in brain, and lung but was also detected in kidneys and the liver in samples prepared from mice injected with either parental or mock transfectant MDA-MD 231 cells (Figure 7b). Despite the reported 10 sensitivity of this assay, which is able to detect 1 human cell/1  $\times 10^6$  mouse cells, no metastasis could be found in the aforementioned organs in mice that were injected with ASHAS2 transfectants (Figure 7) were determined to find any metastasis to soft organs, however, there were no detectable metastases with the HAS2 antisense and significantly 15 high levels of metastasis were found in the brain and lung compared to the kidney and liver in the parental mice groups (Figure 7b).

Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications. The invention also 20 includes all steps, features, compositions and compounds referred to or indicated in this specification individually or collectively, and any and all combinations of any two or more steps or features.

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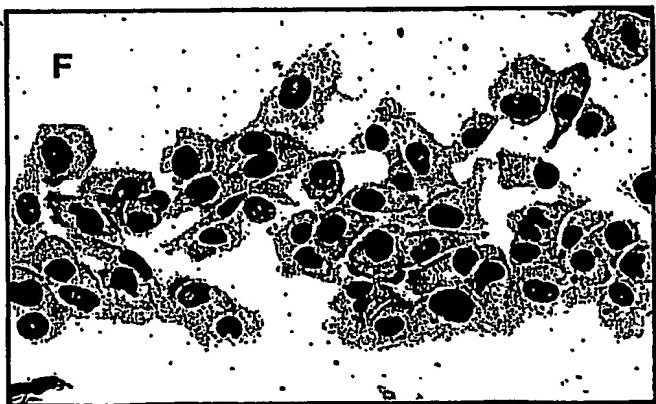
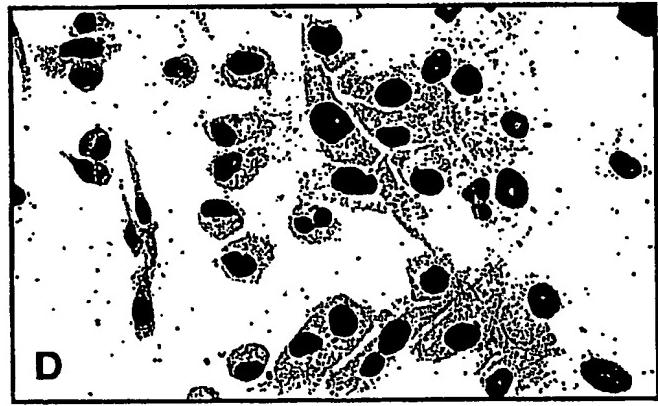
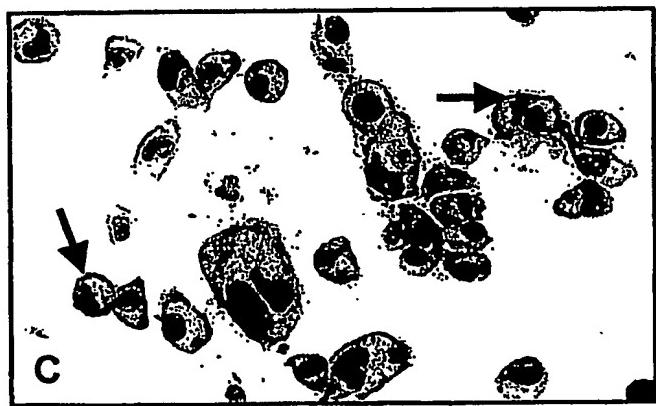
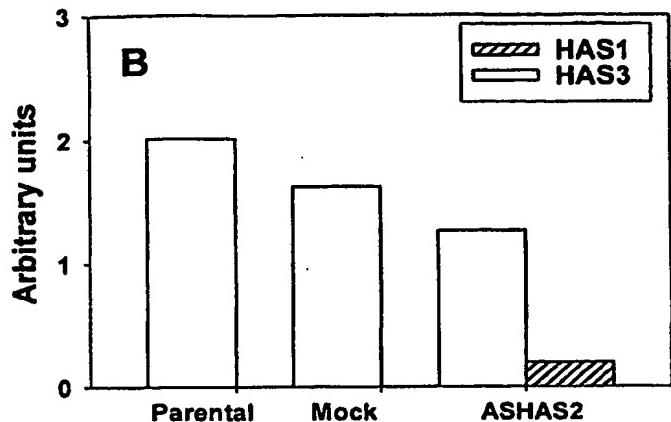
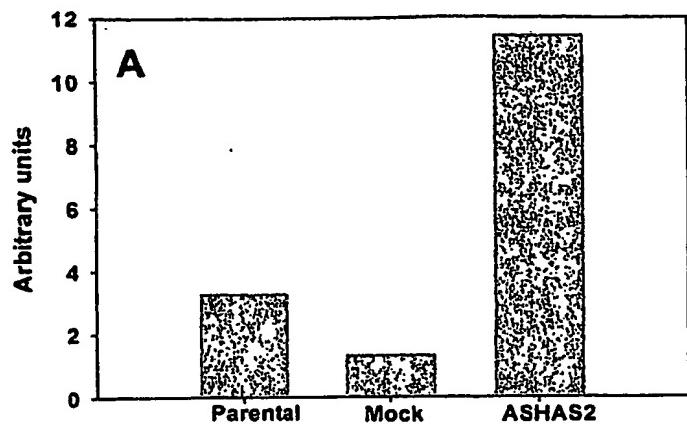
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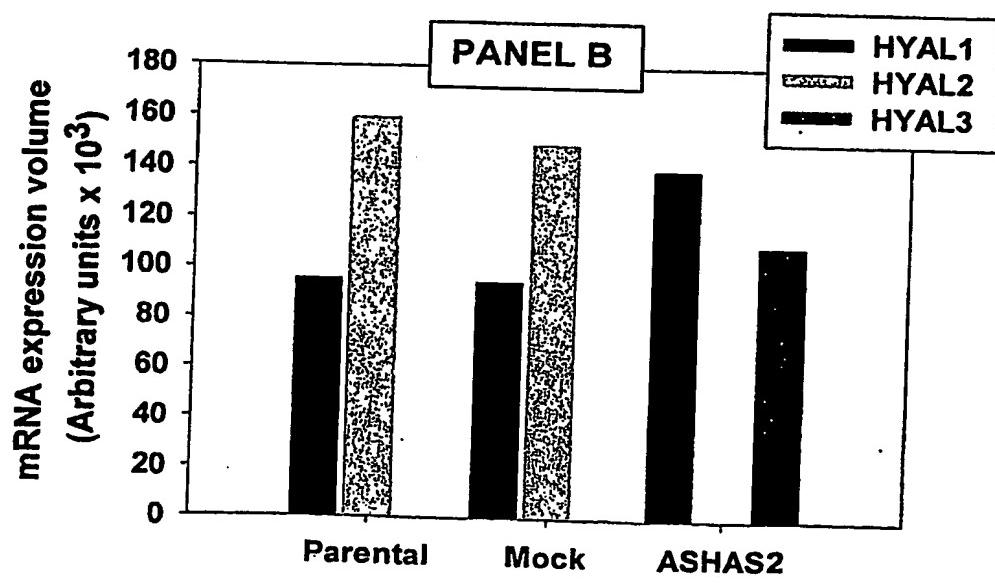
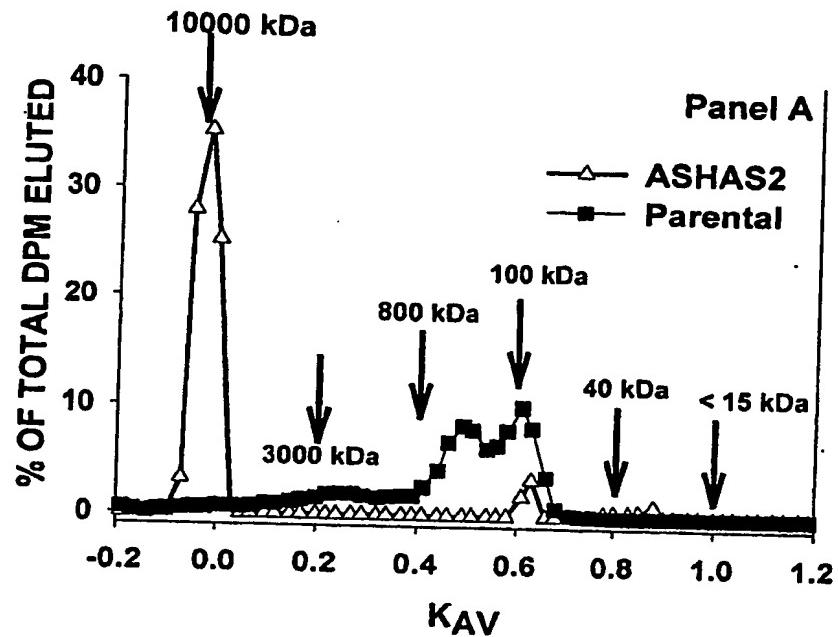
## ABSTRACT

The present invention provides compositions and methods for modulating the expression of genetic material encoding hyaluronan synthase (HAS). In particular, the present invention relates to compounds which hybridize or otherwise interact with nucleic acid molecules encoding HAS and particularly HAS isoforms HAS1, HAS2 and HAS3 or with nucleic acid molecules required for or which facilitate expression of HAS-encoding material thereby reducing expression of the genetic material. These compounds include nucleic acid molecules, ranging in size from oligonucleotides to full length sequences and include complexes comprising RNAi or ribonuclease-type molecules. Such compounds are exemplified to modulate cellular proliferation, and are useful in the prophylaxis and/or treatment of inflammatory disorders, such as but not limited to cancer and arthritis. It will be understood, however, that the compounds can be used for any other condition in which hyaluronan (HA) is involved.

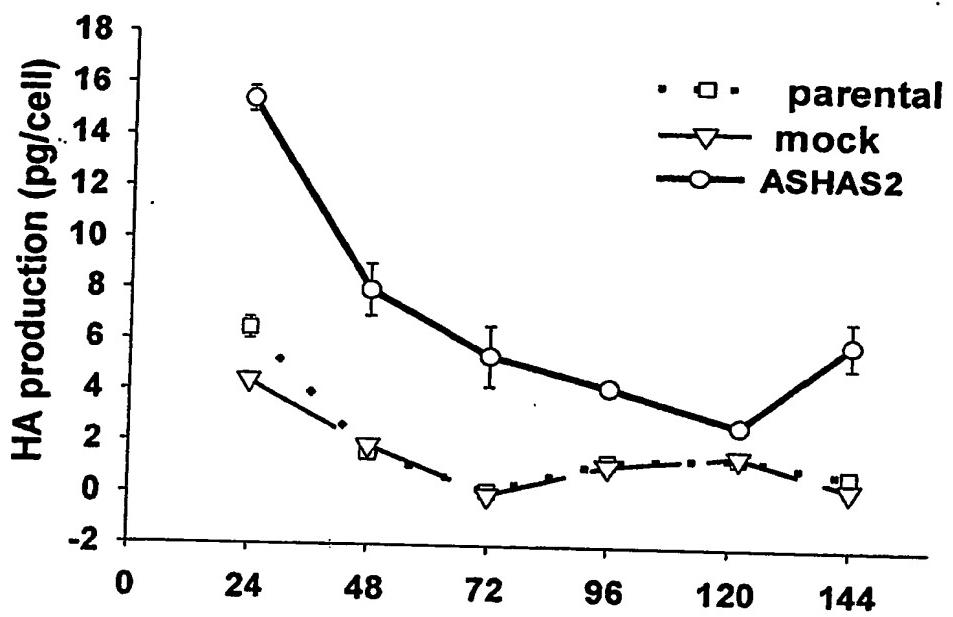
**Figure 1.**



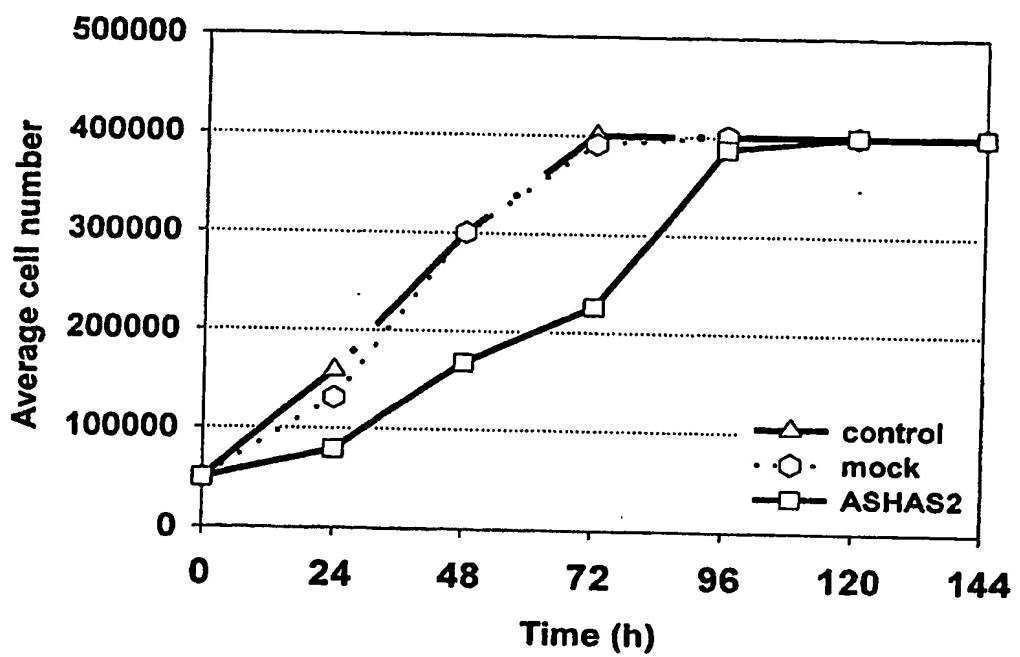
**Figure 2.**



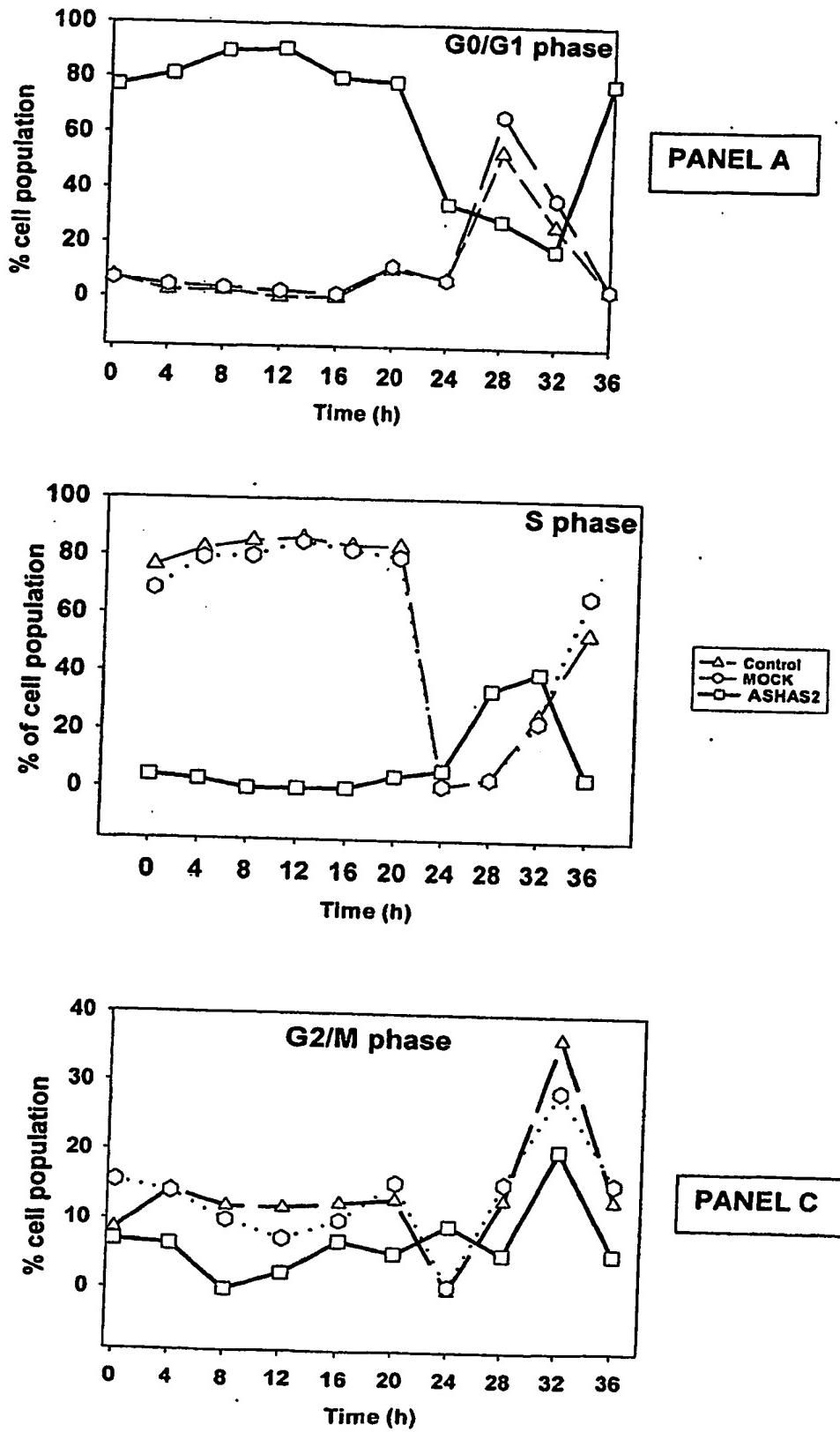
**Figure 3.**



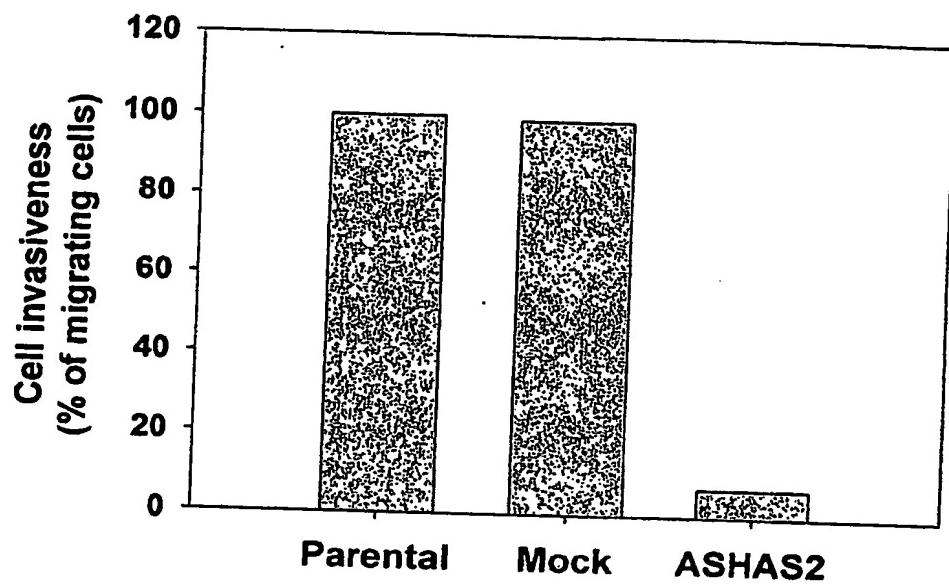
**Figure 4.**



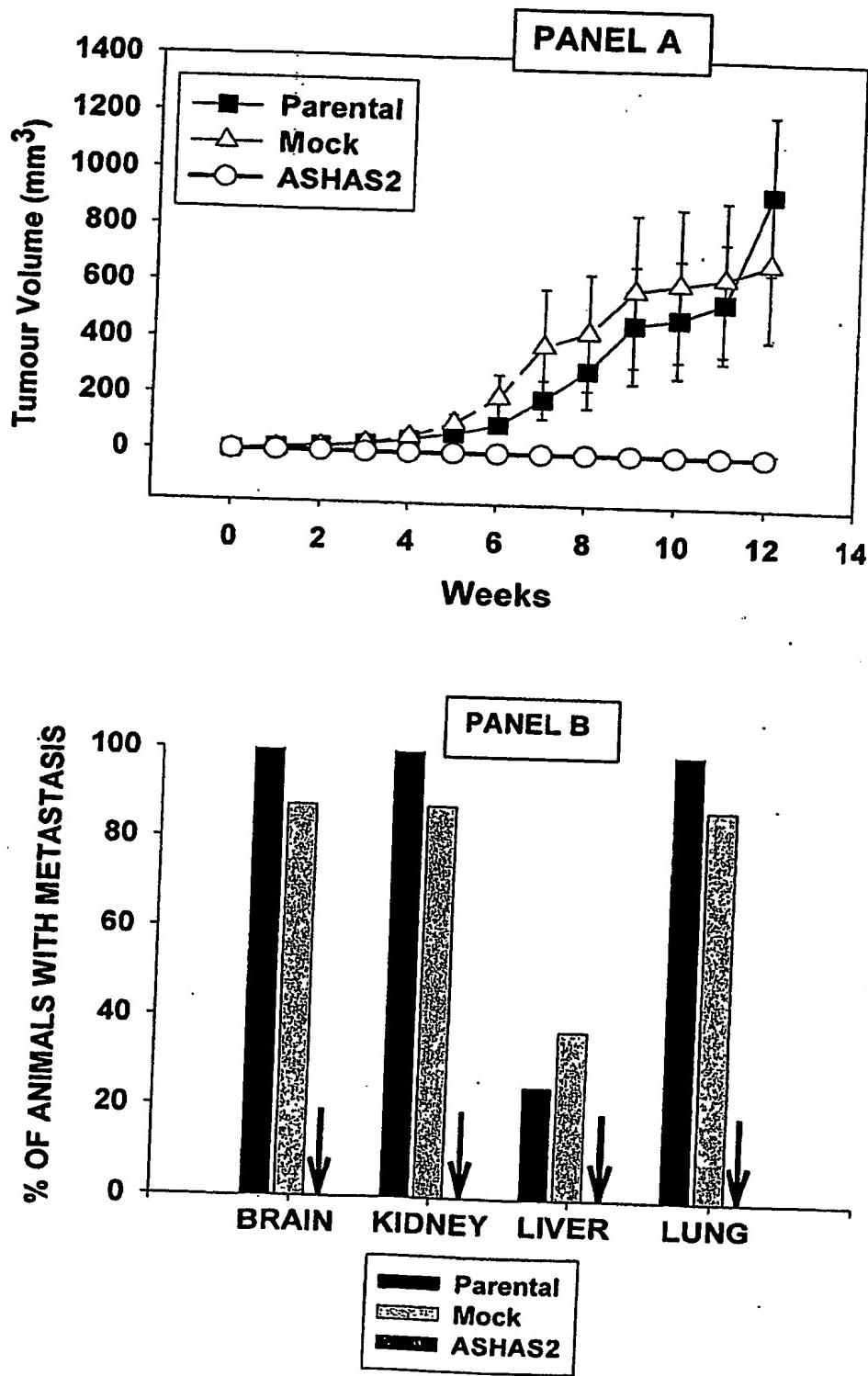
**Figure 5.**



**Figure 6.**



**Figure 7.**



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